Prolonged Epileptic Seizures: identification and treatment

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Setting the scene: definition of prolonged seizures, acute repetitive seizures, and status epilepticus. Do we know why seizures stop?

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ABSTRACT – Status epilepticus is recognised as an acute emergency requiring urgent intervention. The optimal timing of such an intervention during a prolonged seizure, and the reasons for such, have provided much discussion. For operational purposes, a definition of a prolonged seizure of ≥5 minutes requiring intervention appears justified. However, a definition of status epilepticus of ≥30 minutes should stand, with the proportion of seizures proceeding to this clinical state remaining small. The reasons for this may be inherent to an individual, but an understanding of the mechanisms underlying the predisposition may lead to improved management pathways in the future.

Key words: status epilepticus, seizure, prolonged seizure

Historical perspective

Convulsive status epilepticus (SE) is a recognised emergency requiring urgent treatment. The definitions of prolonged seizures and status epilepticus, however, have provided much debate over many years. Early definitions referred to seizures that persisted for hours, if not often days. An early definition by Clark and Prout (1903) referred to "*a state in which seizures occur so frequently that the coma and exhaustion are continuous between the seizures*". Later, Kinnier Wilson referred to such as the severest form of seizures in which "*the post-convulsive sleep of one attack is cut short by the development of the next*" (Wilson, 1940). Later, in the initial classification of the epilepsies, the International League Against Epilepsy (ILAE) defined status epilepticus as prolonged or repetitive seizures, a situation in which "*a seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed or enduring epileptic condition*" (Gastaut *et al*., 1964), and

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this was retained when the classification was revisited in 1970 (Gastaut, 1970). This was subsequently revised a little and defined as a condition characterised by epileptic seizures that are sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition (Proposal, 1981).

The main criticism of the ILAE definition is that it does not define a specific duration, and for the purpose of such a definition was not recognised as requiring to do so. However, many authors have taken 30 minutes as an appropriate cut off for such a definition (Lowenstein *et al*., 1999). The rationale behind this time period was based on the fact that this is the duration of time tolerated prior to cell and neuronal death in certain animal models (Lowenstein *et al*., 1999), after which there is greater risk of decompensation both systemically and within the brain (Lothman, 1990). In practice, such a definition caters for epidemiological study, but does not indicate at which time point treatment is required. Essentially, why do seizures in most circumstances self-terminate? Why in certain circumstances is there a failure of mechanisms required to terminate a seizure? At what point is it evident that this is the case, and should we treat to try and prevent the possibility of the development of full status epilepticus? Evidence suggests that earlier intervention is likely to reduce the subsequent risk of evolution to status epilepticus (Shinnar *et al*., 2001; Chin *et al*., 2008).

Why have treatment and who requires it?

Much of the work outlining the harm of status epilepticus originates from animal studies, notably the work of Meldrum and colleagues and their observations in baboons, as well as observational studies in humans. There has been an ongoing debate as to the effect of prolonged seizures on the hippocampus, and the possible relationship to the development of hippocampal sclerosis and later temporal lobe epilepsy (Liu *et al*., 1995; MacDonald *et al*., 1999). Meldrum determined that following induced status epilepticus of >90 minutes in baboons, neuronal alterations typical of ischaemic cell change were seen diffusely in the neocortex, the cerebellum, and the hippocampus (Meldrum and Brierley, 1973), but that acute hippocampal injury occurred in the absence of local ischaemia and hypoxia (Meldrum *et al*., 1973). Imaging studies of individuals who have experienced status epilepticus have revealed initial oedema with subsequent generalised volume loss of the brain; more specifically, deep grey matter structures appear at risk of injury. Evidence of more diffuse excitotoxic cell injury in children has been determined from post mortem studies (Tsuchida *et al*., 2007). Consequently, an operational definition is required to determine optimal timing of treatment to prevent established status epilepticus where possible.

Studies with video-EEG recordings suggest that the majority of convulsive generalised tonic-clonic seizures terminate prior to two minutes. Jenssen and colleagues evaluated 579 seizures recorded on video-EEG monitoring in 159 adults (Jenssen *et al*., 2006). All the primary and majority of secondary generalised tonic-clonic seizures terminated before 5 minutes; only two of the secondary generalised tonic-clonic seizures lasted longer than 10 minutes. In a further study, 226 prospective SE cases (91 children and 135 adults) from an ongoing epidemiological study and 81 retrospective cases (31 children and 50 adults), lasting >10 and <29 minutes, from a similar two-year period, were compared (DeLorenzo *et al*., 1999). There was no statistically significant difference in the age, gender or ethnic distribution between the two groups. In the prolonged seizure group, 42% of the seizures stopped spontaneously and patients did not receive treatment, whereas the remaining 58% received AED treatment. This was significantly different to the SE group where only a small number stopped prior to AED administration. The mortality of the prolonged seizure group that stopped seizing spontaneously was zero and only 5.8% in the treated group. For the SE group, the mortality rates were 19% and 18% for treated and spontaneous termination, respectively. Consequently, it would appear there is evidence to treat a prolonged seizure, at the very least, at 10 minutes. However, on the basis of these data, as well as the fact that it appears unreasonable to wait for treatment of an individual arriving at an emergency department, a proposal of an operational definition of >5 minutes has now been widely used for working practice (Lowenstein *et al*., 1999; National Institute of Health and Clinical Excellence, 2012). This was originally put forward for adults and older children >5 years, with >5 minutes of continuous seizures or two or more discrete seizures separated by incomplete recovery of consciousness. It was proposed that in view of the unique forms of prolonged seizures in young children and infants, especially febrile seizures, a longer time frame of 10-15 minutes was suggested, however, with the recognition that there was no available data. It would appear illogical, given the susceptibility of the immature brain, for a different definition to be implemented in this age group. It has also been proposed that there should be a separate mechanistic definition for research purposes, a condition in which there is a failure of the "normal" factors that serve to terminate typical generalised tonic-clonic seizures (Lowenstein *et al*., 1999).

Epidemiology

Epidemiological studies have suggested an overall incidence in adults and children of 0.6-1.9/10,000 if a definition of seizure duration >30 minutes is taken (Coeytaux *et al*., 2000; Hesdorffer *et al*., 1998; Knake *et al*., 2001; Wu *et al*., 2002). The Richmond study determined an ethnic difference with an incidence of 4.1/10,000 in a large non-white population, with only 1.8/10,000 if the white population was addressed (DeLorenzo *et al*., 1996). More specifically, in children, a similar incidence of 1.45/10,000 was determined in the North London study (Chin *et al*., 2006), with an ethnically adjusted incidence of 1.15. In the latter study, febrile status and acute symptomatic aetiology were responsible for almost 50% of cases and 12% occurred in individuals with an existing diagnosis of epilepsy.

A further question arises as to the risk of a prolonged seizure being the presentation of new-onset seizures. In a study of 407 children with first unprovoked seizures, seizure duration was determined using a structured interview and review of medical and ambulance records (Shinnar *et al*., 2001). Mean duration of all seizures was 12.2 minutes; seizures lasted ≥5 minutes in 50% cases, ≥10 minutes in 29%, ≥20 minutes in 16%, and ≥30 minutes in 12%. The longer the seizure lasted, the less likely it was to stop within the next few minutes. In the 189 children with two or more seizures, the duration of the first and second seizure was highly correlated. They concluded that the seizure duration in children with a first unprovoked seizure is different to that in children with refractory epilepsy, and that a subgroup of children are predisposed to prolonged seizures. No clear relationship has been determined with duration of seizure, frequency of SE, or treatment (Raspall-Chaure *et al*., 2006; Camfield and Camfield, 2012), however, an underlying cause appears to be most significantly related (Raspall-Chaure *et al*., 2006; Stroink *et al*., 2007; Camfield and Camfield, 2012). The issue remains, therefore, as to why seizures do not terminate in certain individuals. The study discussed above suggests a susceptibility to prolonged seizures in individuals, with two or more subpopulations showing a tendency to SE (Shinnar *et al*., 2001), and further clues arise from twin studies, with concordance demonstrated in identical twins (Corey *et al*., 1998). There is also a degree of syndrome specificity with early SE, a hallmark of Dravet syndrome, as well as other *SCN1A*-related epilepsies. Notably, in this syndrome, the tendency to have prolonged seizures and SE reduces with age, suggesting a dynamic in the susceptibility (Jansen *et al*., 2006). However, with regard to pathophysiology, if a common underlying problem could be determined, novel treatments could be more targeted and consequently more successful. Several mechanisms for seizure termination have been suggested. These may involve neuronal membranes and synapses, the networks involving neurons and interneurons, and even subcortical structures moderating the balance between inhibition and excitation (Lado and Moshé, 2008).

Within a single neuron, prolonged depolarisations with sustained action potential firing may be initiated by a brief depolarising pulse, or maybe the result of sustained excitatory input. Intrinsic mechanisms of seizure termination active in a single neuron include potassium currents activated by ion entry, loss of ionic gradients, and possibly local depletion of energy substrates. At a neuronal network level, depletion of inhibitory neurotransmission (glutamate, GABA), changes in intracellular and extracellular environments, failure of gap junction decoupling, or effects induced by neuromodulators (endocannabinoids, adenosine, neuropeptide Y) have all been reported to be possibly contributory. Finally, the interrelationship between cortical and subcortical structures and the possible influence on seizure generation and propagation has to be taken into account. Computational modelling studies have suggested that there may be a critical point at which seizures continue, regardless of the mechanism discussed above by which they continue to be propagated (Kramer *et al*., 2012). Utilising human EEG data and computational modelling, Kramer and colleagues suggest human brain electrical activity at various spatial scales exhibits common dynamical signatures of an impending critical transition in the approach to seizure termination, whereas activity in SE repeatedly approaches but does not cross the critical transition. This may of course have a genetic or other aetiological basis. Notably, such susceptibility may be enhanced by resistance to antiepileptic treatment that could be inherent or induced; in one individual who died at 21 years of age following SE, having experienced seizures since seven years of age, arising from a left frontotemporal dysplasia, upregulation of drug transporter proteins was demonstrated through immunohistochemistry in both cerebral hemispheres (Sisodiya and Thom, 2003). The finding of such in the normal hemisphere suggests possible induction through the SE, and may explain, in part, super-refractory SE.

Conclusion

Over time, there appears to have been little questioning as to the definition of status epilepticus; a seizure or series of seizures that last for 30 minutes or more without consciousness gained between seizures. Data also suggest that the use of an operational definition is justified for the treatment of prolonged convulsive seizures lasting five minutes or more. The issue

remains, however, as to why seizures do not terminate in certain individuals, and whether study of the mechanisms underlying the failure to terminate seizures may result in novel treatments. Further questions remain, not least: do young children justify a relaxation of the operational definition, how we may better define the relative role of determined mechanisms responsibly for seizure cessation, and how this may be translated to clinical practice. □

Disclosures.
Professor Cross sits on Advisory Boards for Viropharma, Eisai, and GW Pharma, and was on the steering group for the PERFECT study. Remuneration was made to her department.

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