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Status Epilepticus: How to Keep Your Clinical Skills Up to Date

This dire presentation requires prompt and aggressive attention. Here's how to be ready, should the need arise.

Status epilepticus (SE) is considered a neurological emergency. Left untreated (or undertreated), prolonged seizures can cause permanent neurological injury or death. Rapid treatment must be initiated. If initial agents fail, it may be necessary to induce an iatrogenic coma. In any case, the person in status epilepticus must be closely watched, and often requires continuous EEG in order to confirm that the seizures have stopped not only clinically but electrically as well. This article will discuss a few recent studies and offer clinical insights into hands-on management.

Definitions & Classification

Simply put, status epilepticus is a prolonged seizure. More specifically, it is a seizure that lasts more than 30 minutes or recurrent seizures between which full recovery does not occur (and lasting more than 30 minutes). More recently, however, the definition of status epilepticus has been challenged: some have proposed that a cut-off of 10 minutes should be used as the cut-off in defining status epilepticus.[1] This is partly derived from recent data which shows that most seizures spontaneously cease within one to two minutes. In other words, a seizure that lasts five to 10 minutes is already well beyond the usual duration of spontaneous seizures.

However, just as there are many kinds of seizures, there are many types of status epilepticus. SE can be classified according to the seizure onset: partial status epilepticus versus generalized status epilepticus. More often, however, it is classified by its clinical characteristics: either convulsive (overt or subtle motor manifestations) or non-convulsive (no motor manifestations, *i.e.*, electrographic status epilepticus) Below are the classifications described by Treiman et al.[2]

Generalized Convulsive Status Epilepticus (GCSE):

Overt (70 percent of GCSE): This consists of continuous tonic and/or clonic activity with impairment or loss of awareness.

Subtle (30 percent of GCSE): This is less obvious than the overt type, consisting of facial twitching, nystagmoid eye movements, or subtle jerking of the extremities.

Non-Convulsive Status Epilepticus (NCSE):

Complex Partial Status Epilepticus: This type occurs in patients with a history of partial seizures, but can also arise as a result of acute injury (like a new stroke). This type may cause focal motor manifestations (like nystagmus), but can also cause more subtle findings such as confusion, personality changes or psychosis.

Absence (Typical) Status Epilepticus: This occurs in patients with idiopathic generalized epilepsy. As with complex partial status, the clinical symptoms can be subtle, consisting of confusion or personality changes.

Potential Neurological Morbidity

The most serious, and potentially life-threatening, form of status epilepticus is generalized convulsive status epilepticus. As the duration of the GCSE lengthens, the result is higher mortality and neurological morbidity due to neuronal damage and cell death (see Table 1). This has been demonstrated in both humans and animals, and is the motivation behind prompt, aggressive treatment of GCSE. Intravenous medications are the mainstay of treatment. Although some can cause cardiovascular compromise, rapid infusion of medication is needed to arrest the seizures. Careful cardiac and respiratory monitoring must be performed simultaneously. Continuous EEG is also required in order to confirm that the seizure has been stopped.

Whether neuronal injury occurs in non-convulsive SE (partial status or absence status) is less clear.[3] The prognosis in these cases usually depends on the underlying cause of the status epilepticus (see Table 2), as well as patient age, seizure duration and response to treatment. Note that the lowest mortality occurs in people with epilepsy where the cause of status is low serum AED levels.[1] The highest mortality occurs in people who suffer anoxia or multiple medical problems, and in the elderly. Long seizure duration and a poor response to initial treatment are both poor prognostic factors.[1]

The goal of treatment for NCSE is the same: stop the seizure(s). However, as IV treatment is not benign and can cause serious problems, it must be used more carefully in these situations. A recent study showed that patients who were aggressively treated for NCSE fared more poorly than those who were cautiously managed.[3]

Diagnosis

The diagnosis of SE, regardless of the subtype, is usually made first on clinical grounds. Convulsive status is the most "obvious" because of the organized and rhythmic motor movements that occur. Usually, there is an organized pattern to these, where the seizure starts with a tonic phase which is then followed by clonic

Table 1. Incidence and Mortality Rates for Status Epilepticus

Incidence:
- 9.9 to 15.8/100,000 in Europe (Logroscino 2005)
- 10 to 41/100,000 (Treiman 2006)
- 10to 60/100,000 (Walker 2005)
- 18.3 to 41/100,000 in United States (Logroscino 2005)

Incidence of status epilepticus increases with age (Chen 2006):
- 27/100,000 in young adults
- 86/100,000 in elderly

There are 3,000,000 cases of status epilepticus occur worldwide (Treiman 2006).

Mortality:
- Convulsive status epilepticus: 10-20% mortality rate
- Refractory status epilepticus carries a much higher mortality of 48% (Walker 2005)

Mortality is also higher in the elderly (Chen 2006):
- 14% mortality in those 16-59 years old
- 38% mortality in people over 60

It is generally accepted that the mortality is related to the underlying cause and general medical health of the individual with status epilepticus. The more serious the cause (and the more serious the associated medical illness), the worse the prognosis is likely to be.

Table 2. Common Causes of Status Epilepticus

Cause	Percentage
Low serum AED level (in a person known to have epilepsy)	34%
Remote symptomatic causes	24%
Stroke	22%
Anoxia	10%
ETOH/drug withdrawal	10%

Source: Chen JWY and CG Wasterlain. Status epilepticus: pathophysiology and management in adults. Lancet Neurology 2006;5:246-256.

movements that initially are low amplitude, high frequency. Later in the seizure, the movements become high amplitude, and gradually slow in frequency.

When seizures are occurring frequently, but without full recovery in between, the clinical onset and offset may be clear. As the seizure continues, the movements may become more subtle and irregular. Eventually, if the seizure continues, the movements will become "subtle" and can consist of eye movements, facial movements or twitching of only one hand or digit (Table 3). It is at this point that additional testing, such as continuous EEG is needed in order to determine if the seizure is ongoing.

Nonconvulsive status epilepticus is much more difficult to diagnose on clinical grounds. By definition, there are no organized motor manifestations. Instead, the person may present with confusion, personality changes, periodic unresponsiveness or coma. In other words, the person may appear to be encephalopathic, but is in fact having frequent or continuous seizures. In someone who has a history of seizures, now presenting with one of these symptoms, NCSE must be high on the differential diagnosis. In addition, if the physician encounters a comatose patient in the ICU, this diagnosis should be suspected: up to eight percent of comatose persons in the ICU (where no other cause of coma was apparent) were found to be in nonconvulsive status epilepticus once an EEG was obtained.[3]

Treatment

The Veterans Affairs Cooperative Study (1998) carefully assessed four different initial intravenous treatments for GCSE. The groups were identified as being in either overt or subtle GCSE, and were given IV phenobarbital (15mg/kg) vs. IV lorazepam (0.1mg/kg) vs. IV phenytoin (18mg/kg) vs. IV diazepam (0.15mg/kg) *followed by* IV phenytoin (18mg/kg) The results are shown in Table 4. The trial enrolled 570 patients (518 were evaluable), and one-half were over 65 (47.5 percent were over 65 years old). About 85 percent were men. Very stringent criteria were used to measure treatment success: there had to be complete cessation of both clinical and electrical abnormalities within 20 minutes of the infusion, with no recurrence within 40 minutes of the treatment.[4]

The study showed that IV lorazepam, as initial intravenous treatment was more successful than IV phenytoin. There was no difference among the groups for recurrence of seizures (all protected the patients for seizure recurrence equally well). There was no difference in the rates of hypotension between the groups. There were no differences in rates of respiratory or cardiac arrhythmias. Hypotension occurred more often in patients in subtle generalized convulsive status epilepticus, likely reflecting the fact that this group was "sicker." Life-threatening medical conditions such as cardiopulmonary arrest occurred more often in the overt generalized convulsive status epilepticus group.[4]

Overall, the group in subtle generalized convulsive status epilepticus did much worse. The response to initial treatment was much less, and the outcome was poor. This is likely due to the fact that the duration of the subtle generalized convulsive status epilepticus was longer in duration. However, the underlying cause of the status epilepticus was almost certainly a factor as well.[4] Two-thirds of people in overt generalized status responded to first therapy, compared to only one-quarter of those in subtle generalized status.[4]

Table 3. The "Stages" of Generalized Convulsive Status Epilepticus

Impending: Continuous or intermittent seizures lasting more than five minutes, without full recovery between seizures. In this phase, there are usually discrete convulsions where the clinical start and stop is apparent.[1] The EEG shows distinct seizures which have a clear electrographic onset, evolution, and offset.[2]

Established: Clinical or electrographic seizures lasting more than 30 minutes without full recovery between seizures.[1] The ictal discharges on EEG persist; however, the onset and offset of the seizures becomes less distinct.[2]

Subtle: The motor manifestations of prolonged status epilepticus are now more subtle, and may go unrecognized.[1] The EEG shows continuous ictal abnormalities.[2] Although these may wax and wane in either amplitude or frequency, a distinction can no longer be made as to where a seizure begins or ends.

Table 4. Response of GCSE to Treatment

From the Veterans Affairs Cooperative Study 1998

	Generalized Convulsive Status Epilepticus (overt)	Generalized Convulsive Status Epilepticus (subtle)
Treatment	Response	Response
IV phenobarbital, 15 mg/kg	58.2 %	24.2 %
IV lorazepam, 0.1 mg.kg	64.9 %	17.9 %
IV phenytoin, 18 mg/kg	43.6 %	7.7 %
IV diazepam (0.15 mg.kg) followed by IV phenytoin (18 mg/kg)	55.8 %	8.3 %

Source: Treiman DM, Meyers PD, Walton N, Collins JF, Collins C, et al. A comparison of four treatments for generalized convulsive status epilepticus. NEJM 1998;339(12):792-798.

Nonconvulsive status epilepticus is generally treated using the same armamentarium of medications. Initial treatment is usually the same as for GCSE. However, there is some controversy as to how aggressively NCSE must be managed, especially in light of studies that have shown that aggressive management of NCSE results in a poorer outcome.[3] The lesser outcome was due to the side effects of these medications when used in high doses (hypotension, cardiac arrhythmias, etc.). Further study is needed to address the optimal management of persons in NCSE.

Though an important study, the VA trial only addresses the initial treatment of generalized status epilepticus. For patients who do not respond to initial therapy, what is the next step? Should fosphenytoin be given instead of phenytoin? What is the role of intravenous valproate (Depacon) in the treatment of status epilepticus? Unfortunately, these questions remain unanswered.

In 2001, a survey of expert opinion on this matter was conducted[5] to better understand how a group of well-respected physicians might treat generalized status epilepticus, partial status epilepticus or absence status. In all cases, IV lorazepam was selected as the first agent. This was followed by fosphenytoin, which was universally preferred over phenytoin. Following this, the options were less clear, but included IV phenobarbital and IV valproate. Although not a controlled trial, the survey highlighted the use of medications in a "real world" setting.

Regardless of the order in which medications are selected, each hospital should have a protocol for the treatment of status epilepticus.[1] The failure of medications to arrest status epilepticus is often due to delays in initiating treatment, delays between drugs, and timidly applied dosing. In other words, going too slow and too low is a problem when treating status epilepticus. A carefully applied protocol can help physicians to avoid these pitfalls, and improve clinical outcomes.

Conclusions

Regardless of the cause, status epilepticus is a medical and neurological emergency. Rapid diagnosis and treatment are needed. Careful monitoring for possible cardiac and respiratory side effects of treatment is needed during intravenous therapy. Medical testing, such as EEG, is not required to initiate treatment, but will be needed to confirm that the treatment has been successful. Treatment protocols can help physicians to avoid pitfalls of therapy such as delaying the time to treatment and underdosing of medications. When carefully applied, these treatments are usually successful: two-thirds of patients in generalized convulsive status epilepticus will respond to the first administered therapy. **PN**

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