The acute management of seizures in childhood

Rod C Scott

INTRODUCTION

The epilepsies are the most common neurological conditions presenting to general paediatricians and paediatric neurologists. Management usually revolves around trying to prevent seizures from occurring, using a wide variety of antiepileptic medications, and around the management of additional cognitive, behavioural and motor impairments.

As long as seizures are short and self limited this management is appropriate. However, not all seizures terminate spontaneously and in these circumstances emergency rescue therapy may be required. This raises questions relating to definitions of short seizures not requiring therapy, seizures that require treatment but do not meet criteria for the standard definitions of status epilepticus, and the most appropriate definition of status epilepticus. This article will focus on such seizures and will discuss which seizures require treatment, why it is important to treat certain seizures, and the most appropriate management strategies.

DEFINITIONS

For the purposes of emergency management seizures are usually considered to be either convulsive (i.e. tonic–clonic) or non-convulsive. This article will only discuss convulsive seizures.

The usual definition for convulsive status epilepticus is a seizure, or series of seizures without consciousness being regained between the seizures, which lasts at least 30 minutes (Celesia, 1976; Shepherd, 1994). It is widely accepted that seizures that last for 30 minutes require emergency therapy, but it is also widely accepted that seizures should be treated before 30 minutes given that outcome worsens with increasing seizure length. However, the majority of tonic–clonic epileptic seizures are self-limiting, will last less than 2–3 minutes and do not require rescue therapy.

As approximately 95% of seizures that last 7 minutes will last at least 30 minutes (Shinnar et al, 2001), it seems likely that a seizure that lasts 7 minutes is pathophysiologically similar to one that lasts 30 minutes and could be considered to be status epilepticus requiring treatment. For this reason it is frequently advised that children that have had a 5-minute seizure should receive rescue therapy (Scott et al, 1998b), accepting that a few would have had a seizure that would have stopped spontaneously.

Most studies that address the outcomes from convulsive status epilepticus have used a 30-minute definition as data from animal models suggest that brain injury can occur with seizures that have lasted at least this long (Ben Ari, 1985; Cavalheiro, 1995; Meldrum, 1997). Thus, treatment of status epilepticus (with a 5-minute definition) is required in order to reduce adverse outcomes associated with seizures that last at least 30 minutes.

CONVULSIVE STATUS EPILEPTICUS IN CHILDHOOD

Incidence

All epidemiological studies to date that aim to estimate incidence of convulsive status epilepticus have used a 30-minute definition. There are only five epidemiological cohorts that have been reported and these are largely based on adult populations (DeLorenzo et al, 1995; Logroscino et al, 1997; Hesdorffer et al, 1998; Coeytaux et al, 2000; Knake et al, 2001; Logroscino et al, 2002; Wu et al, 2002). Three studies have been carried out in the USA and two have been carried out in Europe. These studies have been systematically reviewed (Chin et al, 2004a).

The incidence ranges from 6.1 to 41 episodes per 100 000 population per year. This wide range can be partly explained by differences in methodology and ascertainment, but the incidence of status epilepticus ranges from 18 to 41/100 000/year even if studies are of similar high quality (Chin et al, 2004a). This may be partly explained by the racial variation of the populations given that the incidence is higher in non-white than white populations.

The North London Status Epilepticus in Childhood Surveillance Study is the only purely paediatric epidemiological study in Europe and preliminary results suggest that the incidence in childhood is 18 episodes/100 000 children/year. Therefore there are approximately 4000 episodes of convulsive status epilepticus in England and Wales every year. In addition to this there must be a large number of children who receive early rescue therapy and whose seizures are terminated before the seizure has continued for 30 minutes. These children will not be included in current estimates of incidence of convulsive status epilepticus. It is therefore likely that doctors working in paediatric accident and emergency departments will need to treat an episode of convulsive status epilepticus several times per year.

Classification

The aetiology can be classified as febrile, acute symptomatic, idiopathic, remote symptomatic, or epilepsy related (*Table 1*).

Outcomes

The possible adverse outcomes from childhood convulsive status epilepticus include subsequent epilepsy, permanent neurological, developmental or cognitive deficits, or even death (Towne et al, 1994). Mortality and morbidity associated with convulsive status epilepticus is largely dependent upon aetiology (Aicardi and Chevrie, 1970; Aminoff and Simon, 1980; Dunn, 1988; Yager et al, 1988; Maytal et al, 1989) and upon seizure length, with increasing seizure length being

Dr Rod C Scott is Lecturer in Paediatric Neuroscience and Honorary Consultant Paediatric Neurologist, Neurosciences Unit, Institute of Child Health, University College London WC1N 1EH

associated with a worse outcome (Dunn, 1988; Maytal et al, 1989).

A mortality of 11% was reported in 1970 (Aicardi and Chevrie, 1970) with an apparent decrease to between 3.6 and 6% by 1989 (Maytal et al, 1989; Phillips and Shanahan, 1989), with almost all the mortality being associated with acute neurological insults or progressive neurological disease. Although this appears to imply that the mortality had decreased during the 20 years between those studies, a change in definition probably also played a role.

In 1970 a definition of 60 minutes was used, compared to the definition of 30 minutes used in the later studies. In adults, 60-minute seizures are more likely to be associated with mortality than seizures lasting 30–60 minutes. The mortality associated with convulsive status epilepticus in children who required admission to an intensive care unit was 9% in 1994 (Lacroix et al, 1994), and given that most children who require intensive care admission as part of treatment for convulsive status epilepticus will have had a seizure that lasted 60 minutes, the mortality from such prolonged seizures does not appear to have altered in the intervening 24 years. This lends support to the hypothesis that mortality is at least in part dependent upon seizure length, but that there will continue to be a mortality associated with the underlying disorder.

Although there are only sparse data related to the functional outcomes from convulsive status epilepticus, they support the view that convulsive status epilepticus is associated with the development of cognitive and neurological impairments. The data on overall cognitive outcomes of convulsive status epilepticus are from patients with the most prolonged events and therefore are not representative of the whole population of patients with convulsive status epilepticus. However, it appears that predictors of poor overall cognitive outcomes include increasing seizure length (Dunn, 1988; Eriksson and Koivikko, 1997; Sahin et al, 2001), aetiology and the presence of structural brain abnormalities (Barnard and Wirrell, 1999).

Interventions that decrease seizure length may therefore reduce morbidity associated with convulsive status epilepticus. In cross-sectional studies on small populations of children with convulsive status epilepticus (including prolonged febrile convulsion) who were neurodevelopmentally normal before the acute episode, up to 6% had cognitive deficits by the age of 10 years (Verity et al, 1993). In addition, speech deficits have been identified in children with a history of prolonged febrile convulsion (van Esch et al, 1996). There continues to be uncertainty about specific cognitive and behavioural consequences of convulsive status epilepticus. Therefore, larger population-based studies are required in order to more fully characterize the developmental, cognitive and behavioural outcome of convulsive status epilepticus in childhood.

TABLE 1.
Definitions of types of aetiology associated with convulsive status epilepticus

Aetiology of CSE	Definition
Prolonged febrile seizure	CSE in a previously neurologically normal child aged between 6 months and 5 years during a febrile (temperature above 38°C) illness, and in the absence of defined CNS infection
Acute symptomatic	CSE in a previously neurologically normal child, within 1 week of an identified acute neurological insult including head trauma, CNS infection, encephalopathy, cerebrovascular disease, and metabolic or toxic derangements
Remote symptomatic	CSE in the absence of an identified acute insult but with a history of a CNS insult more than 1 week before
Acute on remote symptomatic	CSE that occurred within 1 week of an acute neurological insult or febrile illness and occurred in a child with a history of previous neurological abnormality
Idiopathic epilepsy related	CSE that is not symptomatic (see above) and occurred in subjects with a prior diagnosis of epilepsy or when the episode of CSE is the second unprovoked seizure that has led to a diagnosis of idiopathic epilepsy
Unprovoked	CSE that could not be classified into any other group

CSE = convulsive status epilepticus

Association with brain injury

It is probable that some morbidity described above is a consequence of brain injury caused by convulsive status epilepticus. Although brain injury and convulsive status epilepticus can both be caused by the underlying aetiology of an episode of convulsive status epilepticus (e.g. meningitis or traumatic head injury), status epilepticus can itself cause brain injury, particularly to the hippocampus, which is in the mesial temporal lobe (Ben Ari, 1985; Cavalheiro, 1995; Meldrum, 1997).

There is a long-recognized association between convulsive status epilepticus (particularly prolonged febrile convulsion, the most common form of convulsive status epilepticus in childhood) and mesial temporal sclerosis (MTS), the most common structural abnormality identified in patients who require epilepsy surgery (Cavanagh and Meyer, 1956; Babb and Brown, 1993). MTS has characteristic histological and imaging abnormalities in the hippocampus and may be associated with more widespread abnormalities in the temporal lobe.

There is a wealth of data from animal models confirming that convulsive status epilepticus can itself cause hippocampal injury, and that many of these animals will develop seizures consistent with temporal lobe epilepsy. There is also increasing evidence from magnetic resonance imaging studies that convulsive status epilepticus can cause hippocampal injury in humans (Nohria et al, 1994; Tien and Felsberg, 1995; Stafstrom et al, 1996; VanLandingham et al, 1998; Scott et al, 2002, 2003). Studies addressing whether children with evidence of acute hippocampal injury go on to develop temporal lobe epilepsy associated with MTS are underway.

Given that there is good evidence that convulsive status epilepticus that lasts at least 30 minutes is associated with significant mortality and morbidity that is, at least in part, dependent

upon seizure length, it is essential that seizures are treated early in order to try and reduce mortality and morbidity.

Treatment

For treatment purposes the operational definition of convulsive status epilepticus is a seizure that continues for at least 5 minutes. It is important to try and terminate the seizure as soon as possible. The aim should be to terminate the seizure within 45 minutes of arrival into the accident and emergency department, following clear, locally generated guidelines based on national guidelines.

GUIDELINES

Convulsive status epilepticus is a medical emergency and it is important to treat it systematically, according to clear guidelines. This has led to the development of at least two sets of UK national guidelines on the management of convulsive status epilepticus in childhood.

The most widely used guidelines are those produced by the Advanced Paediatric Life Support (APLS) group (2000). These guidelines are widely taught to doctors, nurses and paramedics. An alternative national guideline is that produced by the British Paediatric Neurology Association (BPNA) (Appleton et al, 2000). Although remarkably similar these guidelines are not identical despite both being generated by so-called experts.

Assessment of other guidelines from around the world reveals differences dependent upon local environments and opinions, e.g. although paraldehyde is used in the UK it is not used in North America or in the rest of Europe. This raises the issue of whether national guidelines should be seen as a gold standard, or as a starting point from which local guidelines can be generated.

National guidelines will probably not be appropriate in certain environments, e.g. in areas where there is no access to paediatric intensive care services, the use of lignocaine may be more appropriate than recurrent benzodiazepines or barbiturates as second-line therapy, as it does not cause respiratory depression. Some children may not respond to usual treatments and they should have a personalized treatment protocol.

INITIAL ASSESSMENT

The initial statement in both of the above guidelines relates to the important assessment of airway, breathing and circulation when a child arrives in the accident and emergency department with an episode of convulsive status epilepticus.

Most children do not have underlying respiratory or cardiac abnormalities and thus cardiorespiratory abnormalities identified during convulsive status epilepticus are likely to be a result of the seizure (Scott et al, 1998b). This suggests that treatment is equally as important as assessing physiological changes because treating the seizure is likely to correct the cardiorespiratory insufficiencies.

All children with convulsive status epilepticus should have blood glucose estimation and correction if required. It is also important to determine whether there is an acute symptomatic aetiology that requires treatment in its own right, e.g. meningitis. It is particularly important to consider the diagnosis of meningitis in children with convulsive status epilepticus associated with a fever that lasts for at least 30 minutes. Approximately 1–2% of children with short convulsions and fever have meningitis compared to approximately 10% of children with 30-minute seizures associated with fever (Chin et al, 2004b).

PRE-HOSPITAL TREATMENT

Most episodes of convulsive status epilepticus begin in the community, and as early treatment is likely to reduce morbidity, treatment should be initiated in the pre-hospital setting if possible. The standard pre-hospital treatment is rectal diazepam, which has been used in the UK for many years.

Although rectal diazepam is an effective agent it has many problems when being used in the pre-hospital setting. It may be difficult to administer to wheelchair users or during tonic seizures (Wilson et al, 2004). In addition, it may be considered that giving rectal medication is socially unacceptable, particularly in public places, and teachers and carers are reluctant to administer rectal diazepam for fear of sexual abuse allegations (Scott and Neville, 1999). This has led to the development of agents that can be administered via a more socially acceptable route.

Buccal midazolam is rapidly absorbed into the bloodstream and the brain (Scott et al, 1998a), and is not different to rectal diazepam in terms of efficacy (Scott et al, 1999). Subsequent observational studies support the view that buccal midazolam is an effective agent for treating convulsive status epilepticus (Wassner et al, 2001; Kutlu et al, 2003). Although excessive salivation could result in loss of midazolam administered into the buccal cavity this does not appear to be a problem in practice.

Another alternative to rectal diazepam is nasal administration of midazolam, which has been shown to reduce epileptiform discharges in the electroencephalogram (EEG) (O'Regan et al, 1996) and is similarly effective in terminating seizures as intravenous diazepam (Lahat et al, 2000). Potential problems with the use of nasal midazolam include pain as a consequence of the low pH of midazolam solution. Despite the child being unconscious, it is reasonable to regard pain as a surrogate marker of potential damage to the nasal mucosa. There are, however, no licensed medications for pre-hospital use other than rectal diazepam and therefore buccal or nasal medications still need to be used with caution.

Although it seems obvious that pre-hospital treatment is useful in the management of status epilepticus neither the APLS or BPNA national guidelines give prominence to pre-hospital therapy (Chin et al, 2004c). The APLS guideline is ambiguous about whether to consider pre-hospital treatment as the initial treatment, and the BPNA guideline suggests that pre-hospital therapy should be ignored and treatment begins with the first administration of medicine in the hospital setting.

A recent audit of children with status epilepticus requiring paediatric intensive care unit admission showed that children who received pre-hospital treatment were more likely to receive more than two doses of benzodiazepine and more likely to have respiratory depression than children who did not receive pre-hospital treatment (Chin et al, 2004c).

However, 55% of children who received pre-hospital treatment received an inadequate dose. It is therefore possible that if children received an adequate dose of benzodiazepine in the community, and more than two doses of benzodiazepine because the initial dose is ignored, that the risk of respiratory depression will be unacceptably increased.

Locally generated guidelines should consider these data and be precise about how one uses the information on pre-hospital treatment when it has been administered. In addition, only 51% of children received pre-hospital treatment despite many arriving in the accident and emergency department by ambulance. It is therefore germane to ask why some paramedics are not administering pre-hospital medications to children in convulsive status epilepticus and why inadequate doses are being used when pre-hospital treatment is administered.

HOSPITAL TREATMENT

First-line therapy

It is almost universally accepted that the most appropriate first-line agents are benzodiazepines. Many children receive rectal diazepam on arrival in the accident and emergency department in the UK. However, in the USA intravenous benzodiazepines are recommended unless intravenous access cannot be obtained. It remains uncertain which of these approaches is most appropriate and further studies are required.

The two most commonly used intravenous agents are diazepam and lorazepam (Treiman et al, 1998). Lorazepam is becoming the agent of choice as it has a longer therapeutic half-life than diazepam. Although diazepam has a short therapeutic half-life it has a long elimination half-life. This means that diazepam unbinds from the γ-aminobutyric acid $(GABA)_A$ receptor in the brain soon after administration but is stored in body fat for many hours without offering a therapeutic effect. Administration of recurrent doses of diazepam may overload the stores with subsequent respiratory depression. Lorazepam has a long therapeutic half-life and therefore a recurrent seizure as a result of unbinding of the drug from the receptor is less likely.

Second-line therapy

The most commonly used second-line agents for the treatment of convulsive status epilepticus are paraldehyde and phenytoin. The APLS group suggests that they are given in that order while the BPNA suggest that the two agents should be given together. Although there is clear justification for the administration of rectal paraldehyde in children in whom intravenous access has not been established, this justification is less obvious in children with intravenous access secured. The disadvantages of rectal administration of drugs (intrafaecal administration, expulsion, uncertainties about bioavailability) could be considered to outweigh the advantages when one is certain about administration of intravenous agents. This also needs to be considered in the development of local guidelines.

Phenytoin needs to be administered intravenously under continuous electrocardiography monitoring over approximately 20 minutes, although it is often effective before completion of the infusion. An alternative is fos-phenytoin, which can be administered over 7–8 minutes. As fos-phenytoin has to be metabolized in order to obtain phenytoin, the time it takes for phenytoin to enter the brain may be similar with fos-phenytoin and with phenytoin.

Subsequent therapy

Convulsive status epilepticus that has failed to respond to second-line therapy will almost certainly require rapid sequence induction, most commonly with a barbiturate such as thiopentone. Other agents that have been used in the intensive care setting include propofol, phenobarbitone, etomidate and isoflurane. There are no data that support the use of any of these agents over any of the others. Therefore, treatment is largely experience determined and there is variability among practitioners.

USE OF EEG IN MANAGEMENT OF CONVULSIVE STATUS EPILEPTICUS

There are two major uses for EEG in convulsive status epilepticus:

1. Confirmation of seizure termination
2. Confirmation of the presence of a burst suppression pattern in patients who need intensive care treatment.

Confirmation of seizure termination

Termination of the motor manifestations of convulsive status epilepticus does not necessarily imply that the abnormal brain electrical activity has also stopped. Such electromechanical dissociation is associated with a poor prognosis and it is therefore important not to miss it (Treiman et al, 1998). The only reliable way to identify this phenomenon is to obtain an EEG recording after termination of the motor manifestations. If this were to be done in all children who have required rescue therapy, EEG departments would be overloaded and the rate at which electromechanical dissociation is identified would be low.

Children who recover quickly are extremely unlikely to have a continuing EEG abnormality. Therefore, children who do not regain consciousness as rapidly as expected and those who require intensive care should have at least a single EEG recording. A potential pitfall is over-treating children with long-standing frequent EEG abnormalities who have an episode of convulsive status epilepticus in order to try and remove all epileptic discharges from the EEG.

Confirmation of a burst suppression pattern in the EEG

It has long been suggested that children who require intensive care treatment for convulsive status epilepticus should have doses of the chosen medication that results in a burst suppression pattern in the EEG. This pattern should be maintained for approximately 24 hours before weaning of medication. In practice, many children are only ventilated for a few hours and, as there is morbidity associated with ventilation, it would not be advantageous for an individual child to be ventilated for longer than necessary. Thus, children who are not extubated early should have an EEG. Continuous EEG monitoring may also be helpful, but there are insufficient resources in most hospitals for this to be practical.

CONCLUSIONS

Convulsive status epilepticus is a common condition with a significant morbidity and mortality that may be reduced by early therapy. Treatment is most likely to be successful if a clear guideline, appropriate to the local environment, is followed. HM

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KEY POINTS

- A single definition of convulsive status epilepticus is not useful for all circumstances and needs to be modified dependent upon the situation in which it is to be used.
- Convulsive status epilepticus continues to be associated with significant mortality and morbidity.
- Early appropriate therapy may reduce mortality and morbidity.
- Local guidelines, generated on the basis of national guidelines, are important to ensure appropriate treatment in all local environments.
- Rectal diazepam is frequently given at an insufficient dose and this may increase the likelihood of requiring intensive care.
- No more than two doses of benzodiazepine should usually be administered in the initial phases of treatment.
- It is important to determine whether the child rapidly becomes responsive after termination of the motor manifestations of the seizure. If not an electroencephalogram should be obtained to confirm that the seizure has stopped.