Status epilepticus

Outcome of convulsive status epilepticus: a review

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The outcome of CSE in childhood depends mainly upon the cause but length of seizure may also be important

Convulsive status epilepticus (CSE) is often defined as a convulsion lasting at least 30 min or recurrent convulsions occurring over a 30-min period without recovery of consciousness between each convulsion. This review aims to discuss the relationships between CSE, aetiology, subsequent brain injury and adverse outcomes in childhood.

CSE is the most common childhood neurological emergency, with an estimated incidence of 18–20 per 100 000 children per year.[1] This is much greater than the adult incidence of around 4–6 per 100 000 per year.[1–4] It occurs at similar rates in both boys and girls, incidence being highest in infancy and falling with increasing age. In a recent prospective, population-based study of CSE carried out wholly in childhood, The North London Status Epilepticus in Childhood Surveillance Study (NLSTEPSS), the incidence of CSE was shown to be greatest in children under 1 year of age (51 per 100 000 per year) compared with those aged 1–4 years (29 per 100 000 per year), 5–9 years (9 per 100 000 per year) and 10–15 years (2 per 100 000 per year).[1]

Adverse outcomes after CSE include death, cognitive impairment, permanent neurological deficits and subsequent epilepsy.[5–8] While it is widely accepted that CSE is associated with significant morbidity and mortality, there is controversy over the extent to which these adverse outcomes are the result of the CSE itself and how much they are influenced by factors such as the cause of the CSE, the child's age or treatment of the seizure.

Two main populations of children have episodes of CSE: those who were previously neurologically healthy, with normal neurodevelopment, no neurological deficit and no history of epilepsy and those with neurological problems prior to the episode of CSE.[1] In those who were previously normal, most have a prolonged febrile convulsion (see table 1 for definitions) while the remainder have acute symptomatic CSE, most commonly secondary to central nervous system infection, head injury or electrolyte imbalances including hypocalcaemia and hypomagnesaemia, and hypoglycaemia. Most of those children who were previously neurologically abnormal have cerebral palsy, previous epilepsy or learning disabilities. Therefore, CSE should not be considered as a single disorder but rather as a complication of many disorders each with their own prognosis and risks. The challenge is to determine whether CSE results in adverse outcomes greater than those occurring in children with any given underlying disorder but without a history of CSE.

MORTALITY

Although CSE is more common in children than in adults, the risk of death associated with CSE is significantly lower in children. Current estimates of case fatality associated with CSE in childhood range between 2.7% and 5.2%.[1 9–15] This figure is 5–8% for children who are admitted to paediatric intensive care units.[16–18] In contrast, case fatality is reported as 13% in young adults and 38% in the elderly.[19]

The main determinant of this age-dependent difference in mortality is the difference in causes between adults and children. The most common cause of CSE in childhood is prolonged febrile convulsions, which are generally associated with negligible morbidity and mortality.[2 12 20–23] Although prolonged febrile convulsions are the most common form of CSE in children under 2 years of age, there is also a higher rate of acute symptomatic CSE, with the overall effect that CSE in young children has higher mortality rates (between 3% and 22.5%) than in older children.[21 24–26] Most deaths in hospitalised children with CSE occur in cases where there is an identifiable associated systemic or neurological disease (symptomatic CSE)[12 17 27 28]; mortality is particularly high in cases of CNS infection and acute brain injury or anoxia.[17 29] This is in contrast to the low mortality directly attributable to CSE, as in unprovoked CSE or febrile CSE, which is estimated at around 0–2%.

It is important to recognise that not all children with CSE associated with a fever have a prolonged febrile convulsion but that some will have acute central nervous system infections. In NLSTEPSS, 11/95 (12%) children with CSE associated with a fever had confirmed acute bacterial meningitis. In a further seven, the final diagnosis was viral meningitis. Most of these children did not have overt evidence of meningitis and three died after an initial diagnosis of prolonged febrile convulsion.[1] Therefore, the risk of CNS infection in children with a history of CSE associated with fever is much higher than the 1.2% risk of meningitis in children with short febrile convulsions.[30] It is important that doctors attending to children with prolonged febrile convulsions maintain a high index of suspicion

Table 1 Definitions of types of aetiology of convulsive status epilepticus

Aetiology of SE	Definition
Prolonged febrile convulsion	SE 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	SE in a previously neurologically normal child, within a week of an identified acute neurological insult including head trauma, CNS infection, encephalopathy, cerebrovascular disease, and metabolic or toxic derangements
Remote symptomatic	SE 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	SE that occurred within a week of an acute neurological insult or febrile illness and occurred in a child with a history of previous neurological abnormality. This category included children with cerebral palsy with a febrile illness not of CNS origin, and children with obstructed ventriculo-peritoneal shunts for post-haemorrhagic hydrocephalus.
Idiopathic epilepsy related	SE that is not symptomatic (see above) and occurred in subjects with a prior diagnosis of idiopathic epilepsy or when the episode of SE is the second unprovoked seizure that has led to a diagnosis of idiopathic epilepsy
Cryptogenic epilepsy related	SE that is not symptomatic (see above) and occurred in subjects with a prior diagnosis of cryptogenic epilepsy or when the episode of SE is the second unprovoked seizure that has led to a diagnosis of cryptogenic epilepsy.
Unclassified	SE that could not be classified into any other group

CNS, central nervous system; SE, status epilepticus.
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for meningitis as, without prompt treatment, the risk of death or significant morbidity in these patients is high.

Whether mortality increases with increasing seizure length is debated. Although data from animal models support this view, there are currently no supportive data from children. The data from adults with CSE have produced conflicting results.[10 13 15 21 31–36] Therefore, it remains unclear whether CSE has an additional adverse effect on mortality above that related to cause. To answer this question, future studies should aim to control for the underlying cause and its severity.[21 37] Even with this lack of robust information, it is probably prudent to assume that CSE does have an additional impact on mortality and to continue to treat CSE aggressively.

NEUROLOGICAL, COGNITIVE AND BEHAVIOURAL IMPAIRMENT

Morbidity secondary to childhood CSE includes the development of focal neurological deficits, cognitive impairment and behavioural problems. Most high quality studies report that neurological sequelae occur in less than 15% of children.[38] Again, cause appears to be the main determinant of morbidity. Almost all children found to have neurological impairment after CSE have had acute or remote symptomatic CSE.[34] Of children with symptomatic CSE, new neurological dysfunction occurs in around 20% of cases.[12 39 40] However, in the absence of an acute or progressive neurological disorder, new neurological deficits occur in less than 10% of cases of childhood CSE.[11 12 39–41]

As with mortality the relationship between duration of CSE and neurocognitive outcome remains uncertain because cause is a confounding factor.[42] A number of studies in patients with CSE which have assessed whether adverse outcomes are related to seizure duration have reported positive findings. However, it is not clear at what point duration of seizure might have a substantial effect on outcome; different studies have reported such a time point as being anything between 1 and 24 h.[11 29 40 43–46] Other studies have found that seizure duration is not an independent risk factor when analysed within causal groups.[17 23 39 47] There exist a number of animal studies that suggest that long seizure duration is directly associated with brain injury, raising the issue of whether human studies have ever been adequately powered or whether treatment usually terminates seizures before they have caused brain injury. Studies in developing countries where treatment is not so readily available may be required to definitively answer this question.

It has been suggested that CSE may have a negative impact on intelligence quotient (IQ) and findings in a retrospective hospital-based study of children with idiopathic generalised epilepsy were supportive of this.[48] In contrast, in a prospective population-based study which reported poorer social and educational outcomes in otherwise neurologically normal adults with childhood-onset epilepsy (compared to controls), a history of CSE did not have any additional impact on outcome. Furthermore, a study in monozygotic twins discordant for febrile convulsions found IQ was an average of 7 points lower in the children with febrile convulsions, but there was no correlation between intellectual deficit and duration of seizure.[49] However, this could be due to the limited number of twin pairs studied. Other reports comparing IQ or academic performance in children with febrile or idiopathic CSE to that in healthy controls have shown discordant results. The highest quality studies usually find no correlation,[22 41] whereas others have reported 15–24% morbidity,[23 26 45] the most commonly reported developmental defect being speech deficit.[23] Therefore, although the relationships between seizure length and IQ do not appear to be causative, they have not been adequately elucidated and further research is required.

SUBSEQUENT EPILEPSY

Only 12% of cases of CSE occur in children with pre-existing epilepsy. In most cases an episode of CSE either leads to the diagnosis of epilepsy or is a single event with or without the development of epilepsy at a later stage. There is again a strong relationship between the type of CSE and subsequent epilepsy.[12 14 39 46] Children with previous neurological abnormality and those with acute symptomatic CSE are more likely to develop epilepsy, with recurrent seizures occurring in more than 50% of these children. The most common type of epilepsy following an initial episode of CSE is focal,[9 50–54] but generalised epilepsy, infantile spasms and Lennox-Gastaut syndrome are also reported.[9 50 53] Unilateral CSE associated with a slight fever is common during the initial phases of the severe epilepsy syndrome, Dravet syndrome. It is likely that this initial febrile CSE is simply part of the natural course of the syndrome, although there has been speculation that it may play a role in the causation of the subsequent problems in these children.[65]

Data on febrile CSE, the most common form of CSE in childhood, are controversial. Overall, the evidence suggests that after an initial short febrile convulsion the risk of developing epilepsy is approximately double that of the general population. In these cases the subsequent epilepsy is most likely to be generalised. However, after a prolonged febrile convulsion the risk of epilepsy is much higher, at around 10 times the general population risk.[14] In these children the subsequent epilepsy is more often focal than generalised. However, while some studies have found a significantly greater risk of subsequent epilepsy in children with febrile CSE compared to children with brief febrile convulsions,[14] others have failed to find a significant difference.[20] Differences in inclusion criteria between studies explain in part some of the variability in estimates. In some studies children of all ages or children with abnormal neurological status,[12 14 22 41 56–58] or prior neonatal[56 59] or afebrile convulsions[57] were included as having febrile CSE. Other studies clearly stated that children outside the accepted age range or with any of the above mentioned features were excluded.[16 23] The studies that include children with neurological abnormalities reveal that, when compared with brief febrile convulsions, the risk of epilepsy after febrile CSE is unchanged in neurologically healthy children but is significantly increased (38%) in those with neurological problems.[22 58]

It should be noted that the variance in estimates for the frequency of mortality, cognitive morbidity and the subsequent development of epilepsy is not only dependent upon biological parameters but also on the quality of the studies, with lower estimates for all adverse outcomes being reported in the better quality studies.[38]

There is a long-standing hypothesis that the increase in focal epilepsy following a prolonged febrile convulsion is due to injury to the hippocampus which can then evolve into mesial temporal sclerosis (MTS), the most common structural abnormality identified in patients who undergo epilepsy surgery.[60–62] There is unequivocal evidence from animal models that CSE can cause hippocampal injury and that some of the animals will then develop spontaneous recurrent seizures, supporting the above hypothesis. Prospective MRI-based studies have revealed that a prolonged febrile convulsion is associated with hippocampal oedema[56 63 64] in patients investigated within 48 h of an episode of febrile CSE. This supports the view that a prolonged febrile convulsion can cause a hippocampal insult.[63] Follow-up investigations 4–8 months after the prolonged febrile convulsion revealed increased asymmetry in the hippocampal volumes compared to the initial data. This reduction in

hippocampal volume to or below the normal range would seem to indicate that earlier findings are temporary (ie, oedema) with subsequent injury and neuronal loss (ie, hippocampal asymmetry) following CSE. However, it is also possible that the asymmetry could be due to a return to a pre-existing hippocampal abnormality similar to that found in family members of patients with MTS and a history of prolonged febrile convulsions. To clarify this would require a systematic longitudinal study to characterise the pathological and clinical evolution of these abnormalities. The evidence to date is certainly in favour of there being a causal relationship between prolonged febrile convulsions, hippocampal injury, MTS and the development of temporal lobe epilepsy. If this is the case, then neuroprotective and antiepileptogenic interventions could hold enormous potential in this particular area.

A probable process leading to symptomatic epilepsy consists of an initial insult followed by a latent period, during which epileptogenesis is occurring, before recurrent seizures develop. Epileptogenesis involves neurobiological changes triggered by the insult, including inflammation, acute and delayed neuronal loss, neurogenesis, axonal and dendritic plasticity, angiogenesis and molecular reorganisation of receptors and channels.[65] The key to trying to prevent the subsequent development of epilepsy in these children is to target this epileptogenic process, either by preventing the brain injury via neuroprotective interventions or by preventing the neurobiological changes that predispose the brain to the development of spontaneous seizures.[65]

Current treatment of epilepsy consists of preventing or suppressing seizures but does not involve targeting this epileptogenic process and there is little evidence that any anti-epileptic drug currently in use has antiepileptogenic properties. There is some evidence from animal work that certain agents may be effective at reducing or preventing brain injury after CSE such as mossy fibre sprouting and neuronal death.[66 67] However, the importance of these processes in epileptogenesis remains unclear as the animals in these studies continued to show recurrent seizures despite a reduction in the pathological changes incurred.

Certainly, one of the major challenges for the future in the treatment of epilepsy is to look for ways of preventing epileptogenesis via therapeutic intervention. Currently the search for effective antiepileptogenic compounds for use in humans is in the very early stages, but this is an exciting new field of potentially great clinical significance.

Studies have shown a lack of association between duration of first seizure and risk of subsequent epilepsy.[68–70] The risk of further unprovoked seizures 2 years after a first-ever unprovoked episode of CSE is 25–40%. This is similar to the 37% reported risk after a brief unprovoked first seizure.[69] Prospective studies of children with a first unprovoked CSE seizure show that the risk of seizure recurrence is highest during the first year after CSE, when it stands at around one in six, and tends to decrease with increasing interval from the index seizure.[68 70] Whether prophylactic treatment after a first episode of CSE modifies the risk of subsequent epilepsy has not been addressed. However, studies in children after a first seizure of any length suggest there is no difference in recurrence rates between treated and untreated patients. For this reason the current recommendation is that long-term treatment is not started after a first unprovoked episode of CSE.

THE EFFECTS OF TREATMENT ON OUTCOME

It is generally accepted that early intervention to terminate seizures is beneficial. There is currently little convincing evidence that in humans the length of seizure directly affects outcome, but there is a wealth of animal data indicating that longer seizures are harmful and result in worse outcomes. Furthermore, it has been shown that the longer a seizure continues the more difficult it becomes to treat,[71 72] again supporting the need for prompt intervention. As most CSE begins in the community, the expansion of the use of prehospital therapies is likely to result in fewer children having seizures of sufficient length to be concerning.

Benzodiazepines are recommended agents for prehospital use. Rectal diazepam is still widely used, but buccal midazolam is gaining popularity as an alternative. It is unlicensed for use in children, but there is evidence that it is more effective than per rectum diazepam at terminating seizures.[73 74] It is also often preferred due to the more pleasant route of administration. A safe, effective and socially acceptable form of treatment is likely to improve prehospital treatment.[16]

As current treatments aim to stop and suppress seizure activity, but do not halt the epileptogenic process leading to the development of these seizures, it is likely that future research in this area will focus on the search for agents with antiepileptogenic properties. This would be with the hope that it may become possible to prevent the development of epilepsy after CSE or other acute brain insult.

CONCLUSION

From the existing evidence it can be concluded that the outcome of CSE in childhood is mainly dependant upon the causal factor. However, evidence from animal models suggests that longer seizure duration results in poorer outcome, so it would seem unwise to ignore the fact that this may also be the case in humans. Future studies aiming to clarify the importance of factors such as age, seizure duration and treatment on the outcome of CSE need to control for cause. The great challenge for the future is in establishing what factors determine outcomes after CSE, and also in elucidating the mechanisms by which these processes may be altered.

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