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Status epilepticus in the developing brain: Long-term effects seen in humans

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There is enormous variability in the estimates of frequencies for outcomes following convulsive status epilepticus (CSE) in children; estimates for mortality range from 0–43%, for subsequent epilepsy from 3.5–100%, and for cognitive/behavioral disorders from 0–83% (Raspall-Chaure et al., 2006). It is unlikely that this extreme variability is entirely due to biologic effects. A systematic review of the literature relating to outcomes from childhood CSE revealed that the estimates of all adverse outcomes are lower in higher quality studies supporting the view that CSE may not be as harmful as previously suggested (Raspall-Chaure et al., 2006). However, even the lower estimates are likely to be important and deserve investigation.

Mortality

In the studies of highest quality, the short-term mortality is between 2.7% and 5.2% (Cavazzuti et al., 1984; Maytal et al., 1989; DeLorenzo et al., 1996; Eriksson & Koivikko, 1997; Waterhouse et al., 1999; Sillanpaa & Shinnar, 2002). The most important factor associated with mortality is etiology, and the evidence for increased case fatality in children with longer seizures is weak and usually confounded by etiology. Children with symptomatic CSE are most likely to die (Lacroix et al., 1994; Chin et al., 2006), and those with prolonged febrile seizures or idiopathic CSE are very unlikely to die within 30 days of the acute event (Maytal et al., 1989; Logroscino et al., 1997). Long-term case fatality (up to 10 years after the event) is approximately 3% in children who survived for at least 30 days after the CSE (Logroscino et al., 2002). Children who had their CSE when they were younger than 1 year of age had a long-term mortality of about 16%. Again, it was the children with symptomatic CSE that were most likely to die. No standardized mortality ratios have been reported for children who have had CSE; a statistic that will help in the understanding of whether CSE has long-term implications for mortality. Therefore, although there is a mortality associated with CSE, it is primarily determined by etiology and not by seizure length.

Subsequent Epilepsy

Focal epilepsies are the most common epilepsies identified in children who have had an episode of CSE (Aicardi & Chevrie, 1970; Cavazzuti et al., 1984; Hesdorffer et al., 1998), although generalized epilepsies, infantile spasms, and Lennox-Gastaut syndrome have all been reported (Aicardi & Chevrie, 1970; Cavazzuti et al., 1984; Viani et al., 1987). The overall rate of epilepsy following a first seizure that lasts at least 30 min is 25–40% (Maytal et al., 1989; Eriksson & Koivikko,1997), which is similar to the 37% risk of subsequent epilepsy reported following a first short seizure (Berg & Shinnar, 1991; Shinnar et al., 1996). Again, the risk is highest in the subgroup with acute symptomatic CSE. Therefore, the overall risk of epilepsy is not dependent on the length of the initial seizure and is more likely to be related to the cause.

The risk of epilepsy following prolonged febrile seizures (the most common type of CSE in children) is estimated to be between 4% and 21% (Nelson & Ellenberg, 1978; Verity et al., 1993). The relationship between prolonged febrile seizures and later temporal lobe epilepsy associated with mesial temporal sclerosis (MTS) is important, because if this relationship were causative then the incidence of epilepsy following a prolonged febrile seizure could potentially be reduced by intervening with neuroprotective and/or antiepileptogenesis strategies (Raspall-Chaure et al., 2006). There is wealth of evidence from animal models supporting the view that CSE can cause hippocampal injury that matures into a disorder resembling human MTS. In humans there is evidence for acute hippocampal injury following prolonged febrile seizure (VanLandingham et al., 1998; Scott et al., 2002, 2003, 2006) and some data suggesting that early magnetic resonance imaging (MRI) findings may provide a biomarker for permanent hippocampal injury (Provenzale et al., 2008). Although the retrospective data from epilepsy

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surgery programs provide evidence for a relationship between prolonged febrile seizure and MTS (Cendes et al., 1993; Trinka et al., 2002), prospective evidence is still poor, although there are ongoing studies that could provide the required definitive evidence.

Cognitive/Behavioral Problems

This is an area that has so far been under-researched, and only two reported studies have used standardized neuropsychological testing in a systematic way (Nelson & Ellenberg, 1978; Verity et al., 1993). Cause, again, emerges as the main determinant of these morbidities. Although adverse outcomes have also been associated with longer seizure durations and with younger age at the time of CSE (Annegers et al., 1987; Dunn, 1988; Yager et al., 1988), it is uncertain whether these effects are independent of etiology. There are long-term adverse social and educational outcomes in children with epilepsy. In one study, which was prospective, there was no additional impact of CSE (Singhi et al., 1992; Sillanpaa & Shinnar, 2002), whereas in another study, which was retrospective and hospital based, the major determinant of intelligence quotient (IQ) in children with ''generalized idiopathic epilepsy'' was a history of CSE (Singhi et al., 1992).

Therefore, further work that defines the relationships between long-term outcomes, etiology, and CSE is required before strategies that minimize the adverse outcomes following CSE can be devised. This is likely to be most rigorously carried out by systematic long-term prospective follow-up of population-based cohorts of children who have had an episode of CSE.

Acknowledgment

I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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