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Death within 8 years after childhood convulsive status epilepticus: a population-based study

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The risk of long-term mortality and its predictors following convulsive status epilepticus in childhood are uncertain. We report mortality within 8 years after an episode of convulsive status epilepticus, and investigate its predictors from a paediatric, prospective, population-based study from north London, UK. In the current study, we followed-up a cohort previously ascertained during a surveillance study of convulsive status epilepticus in childhood. After determining the survival status of the cohort members, we defined cause of death as that listed on their death certificates. We estimated a standardized mortality ratio to compare mortality in our cohort with that expected in the reference population. Multivariable Cox regression analysis was used to investigate any association between the clinical and demographic factors at the time of status epilepticus and subsequent risk of death. The overall case fatality was 11% (95% confidence interval 7.5–16.2%); seven children died within 30 days of their episode of convulsive status epilepticus and 16 during follow-up. The overall mortality in our cohort was 46 times greater than expected in the reference population, and was predominantly due to higher mortality in children who had pre-existing clinically significant neurological impairments when they had their acute episode of convulsive status epilepticus. Children without prior neurological impairment who survived their acute episode of convulsive status epilepticus were not at a significantly increased risk of death during follow-up. There were no deaths in children following prolonged febrile convulsions and idiopathic convulsive status epilepticus. A quarter of deaths during follow-up were associated with intractable seizures/ convulsive status epilepticus, and the rest died as a complication of their underlying medical condition. On regression analysis, presence of clinically significant neurological impairments prior to convulsive status epilepticus was the only independent risk factor for mortality. In conclusion, there is a high risk of death within 8 years following childhood convulsive status epilepticus but most deaths are not seizure related. Presence of pre-existing clinically significant neurological impairments at the time of convulsive status epilepticus is the main risk factor for mortality within 8 years after the acute episode. The attributable role of convulsive status epilepticus on mortality remains uncertain, but appears less than is generally perceived.

Introduction

Convulsive status epilepticus (CSE) is the most common medical neurological emergency in childhood, and is associated with significant short-term morbidity and mortality (Chin *et al.*, 2004; Raspall-Chaure *et al.*, 2006). However, the risk of and predictors of long-term mortality remain uncertain. Reduction of mortality requires identification of such predictors so that strategies that minimize the risk of death can be developed. Mortality within 30 days of an episode of CSE due to all causes has previously been reported to be between 2.7% and 5.2%, but there are no data on mortality following childhood CSE beyond this period (Raspall-Chaure *et al.*, 2006). Previous studies on childhood-onset epilepsy have reported that status epilepticus does not significantly increase the risk of death during follow-up, but these studies did not include children with CSE who did not have a diagnosis of epilepsy (e.g. prolonged febrile convulsions and acute symptomatic CSE) (Sillanpaa and Shinnar, 2002; Stroink *et al.*, 2007).

Much of what is known about the outcomes following CSE in childhood is from hospital-based studies or from population-based studies that include both adults and children, which may not reflect the true picture of CSE in the general childhood population (Logroscino *et al.*, 2002; Raspall-Chaure *et al.*, 2006). Existing literature suggests that there is an association between short-term mortality following CSE and clinical factors at the time of the episode, including aetiology, age, duration and character (intermittent or continuous CSE) (Raspall-Chaure *et al.*, 2006; Sadarangani *et al.*, 2008). Whether any of these clinical factors or demographic features has any association with longer term mortality is yet to be determined.

Our group carried out the first population-based study restricted to CSE in childhood, the North London Convulsive Status Epilepticus Surveillance Study (NLSTEPSS), and found that the incidence, aetiology and short-term mortality are different in children compared with adults (Chin *et al.*, 2006). There were 219 survivors beyond their acute hospital admission for CSE and we have contemporaneous demographic and clinical data that were obtained during their episode of CSE for all children. In an ongoing study, the Status Epilepticus Outcomes Study (STEPSOUT), we are now following up this unique cohort in order to determine the frequency of adverse outcomes, including mortality, and to identify factors that predict those outcomes. In this article, we report on mortality within 8 years after CSE and investigate the factors associated with mortality.

Patients and methods

STEPSOUT involves follow-up of the 226 children ascertained during NLSTEPSS. The details of recruitment during NLSTEPSS have been reported elsewhere (Chin *et al.*, 2006). In summary, over a 2-year period and using a multi-tiered notification system set up within a collaborative network of 21 hospitals, north London children with CSE were identified by their local paediatrician and the linked-anonymized clinical and demographic data shared with the central research team.

In the current follow-up study, subjects are being enrolled through local collaborators within the original collaborative north London network. For each subject, NLSTEPSS identification numbers were used to recall patient identifiable information. The survival status of each child was determined by examining their hospital records and confirmed by checking their survival status on the NHS Care Records Service, to ensure that all deaths in our cohort are accurately recorded. Care Records Service is a national electronic record-keeping service that maintains up-to-date demographic and key health information, including survival status, for all users of the NHS (www.nhscarerecords.nhs.uk). Death certificates of all deceased children were obtained from the UK General Register Office (www.gro.gov.uk), with date of death and cause of death defined as stated on the certificates. Clinical background data on each subject in the study were obtained from the original NLSTEPSS database.

We took a pragmatic decision to keep the diagnostic categories for CSE as classified at the time of CSE and not change the categories according to the information acquired later during the follow-up. This is because the follow-up clinical information is not yet available on all the subjects, and clinical prognostication would be based on the information available at the time of CSE.

Statistical analysis

The mortality rate in our cohort was compared with that expected in the population of north London matched for age to estimate a standardized mortality ratio (SMR). Case fatality was determined as the number of deaths within the cohort during the follow-up period divided by the total number of children in the cohort. The number of person-years of follow-up was calculated for all participants in the cohort. Mortality rate was estimated as the death rate per 1000 person-years of follow-up for study subjects. The data for calculating mortality in the reference population (population estimates from 2002 to 2009) were obtained from the UK Office for National Statistics (www.ons.gov.uk). SMR was calculated as the observed number of deaths in the study cohort divided by the expected number of deaths during the same time period in the age-matched population of north London. The 95% confidence interval (CI) of the SMR was calculated using a standard Poisson-based method.

All statistical analyses were performed on SPSS version 19.0, and StatXact version 4.0 using a complete case analysis approach. After initial descriptive analysis, we used Cox regression analysis to estimate survival following CSE and to investigate the predictors of mortality. We used difference in proportions and Mann–Whitney U test for comparing the follow-up cohort with those lost to follow-up.

To investigate the clinical and demographic factors associated with increased mortality, the subjects were grouped on the basis of presence or absence of clinically significant neurological impairment (motor and/or cognitive) prior to CSE. Children with pre-existing clinically significant neurological impairments, with or without epilepsy, at the time of CSE (i.e. those with remote symptomatic or cryptogenic CSE) were incorporated into Group 1. Those who had no prior neurological

impairments or had epilepsy without additional neurological impairments (i.e. those with prolonged febrile convulsions or acute symptomatic or idiopathic or unclassified CSE) were incorporated into Group 2.

We used Cox regression analyses to identify any factors significantly associated with death as the outcome and clinical and demographic factors as risk factors. Factors significantly associated with the outcome on univariable analysis were then entered in the multivariable models to test their independent association. Any factors not reaching a significance level of 10% ($P \leqslant 0.1$) on univariable analysis were subsequently included in the final multivariable model to identify any factors that were associated with the outcome only after adjustment for other factors. The demographic factors examined were age at CSE, gender, ethnicity and Index of Multiple Deprivation (2004) scores as indicator of socio-economic status (Chin *et al.*, 2009). The higher the Index of Multiple Deprivation score, the more socio-economically deprived are the subjects. The clinical factors investigated were first-ever CSE (incident) versus a past history of CSE, duration of CSE (30–60 min versus >60 min), intermittent versus continuous CSE, type of CSE (focal versus generalized onset) and presence or absence of clinically significant neurological impairment prior to CSE (Group 1 versus Group 2).

Ethics

The study is approved by the UCL Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee.

Results

Of the 226 children ascertained during NLSTEPSS, 20 were lost-to-follow-up, and therefore information on the survival status was available for 206 (91%, 95% CI 87–94%). The clinical and demographic characteristics of the 20 children lost to follow-up were similar to those in which survival data were available with the exception that those lost to follow-up were less socio-economically deprived (median Index of Multiple Deprivation 2004 score of 35.66 in follow-up and 28.72 in lost to follow-up) (Table 1).

In the 206 children on whom survival information was available, 52% were male and 57% had no clinically significant neurological impairment prior to CSE. In most, the episode of CSE at inclusion in NLSTEPSS was their first ever (incident) CSE (78%), was >60 min in duration (61%) and was of generalized seizure type (63%) (Table 1). The median duration of follow-up was 93.66 months (range 0.03–104.3).

Twenty-three children (12 male) died within 8 years of their episode of CSE (case fatality = 11%, 95% CI 7.5–16.2%; mortality rate = 15.37/1000 person-years, 95% CI 10.3–23.0). Seven children died during the hospital stay for their episode of CSE (within 30 days) (short-term case fatality = 3%, 95% CI 1.5–6.2), and the remaining 16 during follow-up. For the 30-day survivors, the overall median time to death following an episode of CSE was 52.8 months (range 1.0–88.8). Three of the seven children who died during the acute period had acute symptomatic CSE (acute bacterial meningitis) and the remaining four had remote symptomatic CSE (progressive neurological disorders). The diagnostic category of CSE in those who died during the follow-up were remote symptomatic (*n* = 12), cryptogenic (*n* = 3) and acute symptomatic

(*n* = 1). There were no deaths in the children who had prolonged febrile convulsions or idiopathic CSE.

The SMR was 46.1 (95% CI 28.6–70.5) for the whole cohort compared with the reference population of north London, and was 30.8 (95% CI 16.8–51.6) for 30-day survivors (Table 2). In children with pre-existing clinically significant neurological impairments (Group 1), the SMR was 91.4 (95% CI 53.2–146.3), and in those with no pre-existing impairments (Group 2), it was 14.8 (95% CI 4.0–37.9). The mortality in 30-day survivors with no pre-existing impairments was not significantly different from the reference population (SMR 3.7, 95% CI 0.1–20.6).

On Cox regression, factors that significantly predicted mortality on univariable analysis were presence of clinically significant neurological impairment prior to CSE [hazard ratio (HR) 6.7 95% CI 2.3–19.7, *P* = 0.001] and previous history of CSE at the time of presentation (HR 2.7, 95% CI 1.18–6.2, *P* = 0.018). On multivariable analysis, the only statistically significant predictor of subsequent mortality was the presence of clinically significant neurological impairment prior to CSE (Table 3).

Among the 30-day survivors, deaths were observed from 1 month after the episode of CSE in those with pre-existing neurological impairments, and occurred at regular intervals throughout the follow-up. In contrast, the only death in the child with acute symptomatic CSE occurred 5 years following the episode of CSE (Fig. 1). The survival estimates for individual diagnostic categories of CSE show that the life expectancy is most severely affected in children with an underlying progressive neurological disorder with ~80% of them not surviving for 20 months after the episode of CSE (Fig. 2). This is followed by cryptogenic CSE and remote symptomatic CSE. Most deaths in acute symptomatic CSE occurred within 30 days of an episode of CSE.

The causes of death as stated on their death certificates and the diagnostic category of CSE are listed in Table 4. A post-mortem examination was performed on three children (13%). All three deaths within 30 days in children with acute symptomatic CSE were due to complications of the underlying cause (acute bacterial meningitis). Only one child who had acute symptomatic CSE died during follow-up (5 years after the index episode of CSE), and the certified primary cause of death was status epilepticus. Among those with remote symptomatic CSE, the primary certified cause of death was respiratory complications (*n* = 5), small bowel complications (*n* = 2), intractable seizures/status epilepticus (*n* = 2), acute complications of underlying medical condition (*n* = 2) and the underlying medical condition/diagnosis (*n* = 5). In those who had cryptogenic CSE, one each was certified to have died due to status epilepticus, severe sepsis and sudden cardiac death with myocarditis.

Discussion

This is the first paediatric population-based study reporting mortality beyond 30 days following an episode of CSE. The main findings of our study are that: (i) children with CSE are 46 times more likely to die within 8 years after their CSE compared with the rest of the unaffected population; (ii) a history of pre-existing neurological impairment, with or without accompanying epilepsy,

Table 1 Clinical and demographic characteristics at the time of CSE of the follow-up cohort and those lost to follow-up

Characteristic	Followed-up (%), n = 206	Lost to follow-up (%), n = 20	Difference in proportion, (95% CI)
Gender			
Male	107 (52)	10 (50)	0.02 (−0.19 to 0.23)
Female	99 (48)	10 (50)	
Median age at CSE, months (range)	32.3 (1–192)	52 (6–177)	0.076*
Clinically significant neurological impairment prior to CSE			
Present (Group 1)	89 (43)	8 (40)	0.03 (−0.19 to 0.22)
Absent (Group 2)	117 (57)	12 (60)	
Diagnostic category of CSE			
Prolonged febrile convulsions	45 (22)	5 (25)	−0.03 (−0.25 to 0.12)
Acute symptomatic	35 (17)	1 (5)	0.12 (−0.07 to 0.19)
Idiopathic	23 (11)	5 (25)	−0.14 (−0.36 to 0.01)
Cryptogenic	9 (4.5)	0 (0)	0.04 (−0.2 to 0.08)
Remote static	72 (35)	7 (35)	0.0 (−0.22 to 0.18)
Remote progressive	8 (4)	1 (5)	−0.01 (−0.2 to 0.04)
Unclassified	14 (6.5)	1 (5)	0.02 (−0.17 to 0.07)
CSE occurrence			
First-ever (Incident)	160 (78)	15 (75)	0.03 (−0.12 to 0.25)
History of CSE (Recurrence)	46 (22)	5 (25)	
Seizure duration			
30–60 min	81 (39)	12 (60)	−0.2 (−0.4 to 0.02)
>60 min	125 (61)	8 (40)	
Seizure character			
Continuous	102 (49.5)	9 (45)	0.05 (−0.17 to 0.25)
Intermittent	104 (50.5)	11 (55)	
Seizure type			
Focal	17 (8)	1 (5)	0.03 (−0.15 to 0.09)
Secondarily generalized	59 (29)	6 (30)	−0.01 (−0.24 to 0.15)
Primary generalized	130 (63)	13 (65)	−0.02 (−0.20 to 0.20)
Ethnicity			
White	76 (37)	9 (45)	−0.08 (−0.30 to 0.12)
Black	36 (17)	6 (30)	−0.119 (−0.35 to 0.04)
Asian	64 (31)	5 (25)	0.06 (−0.16 to 0.21)
Mixed	13 (6)	0 (0)	0.06 (−0.10 to 0.10)
Other	17 (8)	0 (0)	0.08 (−0.08 to 0.13)
Socio-economic status			
Median Index of Multiple Deprivation 2004 scores	35.66	28.72	0.048*

*P-value on Mann–Whitney U test.

Table 2 Mortality in children following an episode of convulsive status epilepticus

	Follow-up (person-years)	Mortality for the whole cohort			Mortality for 30-day survivors		
		Observed[a]	Expected	SMR (95% CI)	Observed[a]	Expected	SMR (95% CI)
Overall	1495.8	21	0.455	46.1 (28.6–70.5)	14	0.455	30.8 (16.8–51.6)
Children with neurological impairment prior to CSE	610.9	17	0.186	91.4 (53.2–146.3)	13	0.186	69.9 (37.2–119.5)
Children without neurological impairment prior to CSE	884.9	4	0.27	14.8 (4.0–37.9)	1	0.27	3.7 (0.1–20.6)

a Two deaths that occurred in 2010 were not included in SMR calculation as the vital statistics for the reference population for the year 2010–11 are not yet available.

at the time of CSE (remote or cryptogenic CSE) is a major risk factor for death with no evidence that other clinical or demographic factors increase risk of death; (iii) there were no deaths following prolonged febrile convulsions and idiopathic CSE; (iv) cardio-respiratory complications and/or intractable seizures are the most commonly reported causes of death; and (v) the attributable role of CSE itself on mortality, rather than the underlying cause of CSE, could be less than generally perceived.

Table 3 Regression analysis for predictors of death within 8 years following an episode of CSE

Variable	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Pre-existing clinically significant neurological impairment at the time of CSE	6.7 (2.3–19.7)	0.001	6.7 (2.3–19.7)	0.001
Gender (male versus female)	0.99 (0.43–2.24)	0.98	–	–
Ethnicity (white, black, Asian, other)	1.05 (0.43–2.6)	0.51	–	–
Socio-economic status (IMD, 2004)	1.0 (0.98–1.04)	0.618	–	–
Age at CSE (months)	1.02 (0.92–1.14)	0.689	–	–
Previous CSE at presentation (recurrence versus incident)	2.7 (1.18–6.2)	0.018	1.8 (0.77–4.3)	0.173
Duration of CSE (30–60 min versus >60 min)	1.91 (0.75–4.8)	0.173	–	–
Character of CSE (continuous versus intermittent)	1.08 (0.47–2.44)	0.858	–	–
Type of CSE (focal versus generalized onset)	1.36 (0.56–3.3)	0.499	–	–

IMD = Index of Multiple Deprivation.
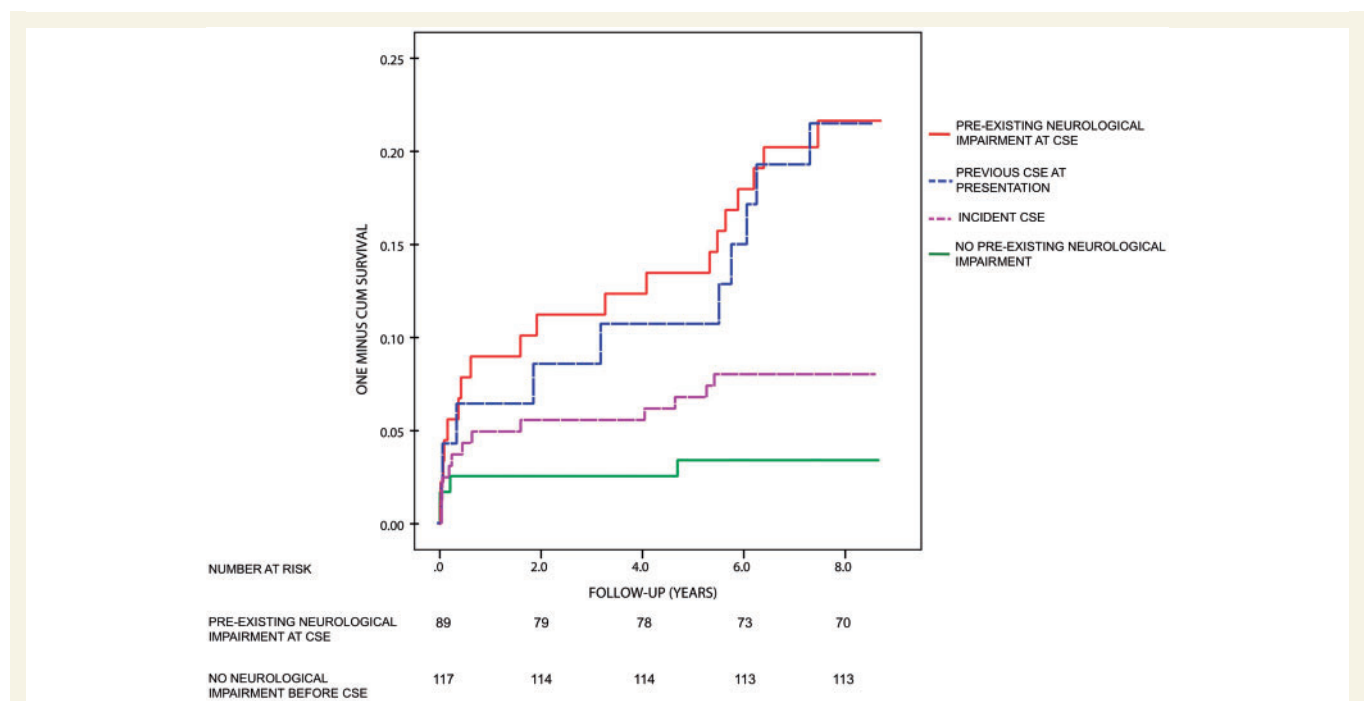
Figure 1 Cumulative risk of death following an episode of CSE according to presence of pre-existing neurological impairment at the time of CSE (survival curves according to presence or absence of previous CSE are superimposed for comparison).

Although the overall mortality in our cohort was 46 times higher than expected in the reference population, this effect was predominantly seen in children with pre-existing clinically significant neurological impairments at the time of CSE (remote symptomatic and cryptogenic CSE). Almost all deaths in children with acute symptomatic CSE occurred within 30 days of their episode of CSE, and those who survive beyond this period were not at a significantly increased risk of death compared with the reference population.

The overall risk of death following CSE was almost seven times higher in children with pre-existing neurological impairments (motor and/or cognitive) compared with those who were previously neurologically normal; and this risk increased to 19 times in those who survived beyond 30 days of their episode of CSE. All deaths in previously neurologically normal children occurred in those with acute symptomatic CSE; three children with acute bacterial meningitis died during the acute episode and one with viral encephalitis died 5 years later. There were no deaths in children following prolonged febrile convulsions, an observation similar to the previous reports of very low risk of mortality following prolonged febrile convulsions, and similar to the mortality in simple febrile seizures (Verity *et al.*, 1993; Logroscino *et al.*, 2002; Vestergaard *et al.*, 2008).

We found that none of the clinical and demographic factors at the time of CSE were independent predictors of subsequent mortality except pre-existing neurological impairment. Previous studies
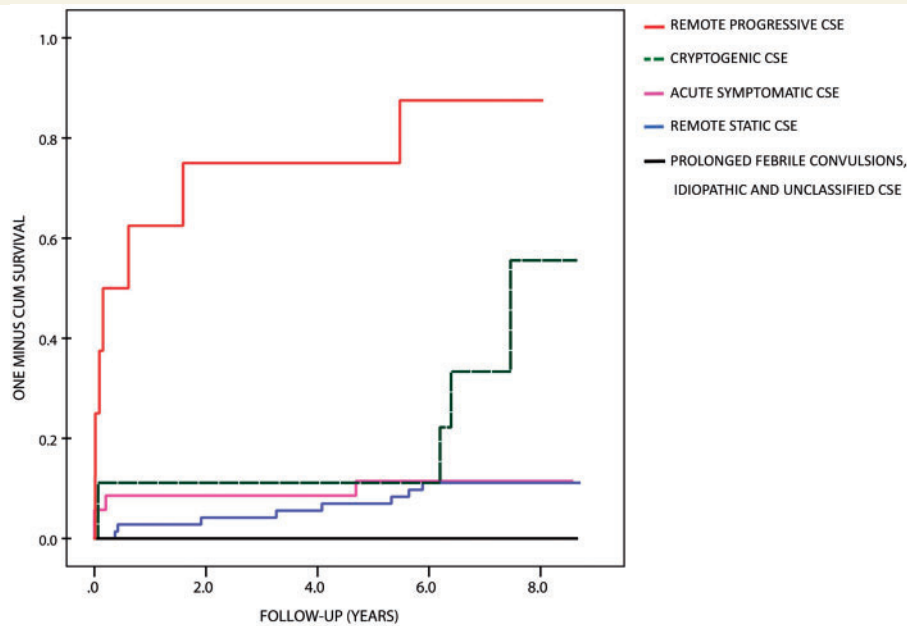
Figure 2 Cumulative risk of death following an episode of CSE according to the diagnostic category of CSE, showing that the life expectancy is most severely affected in children with an underlying progressive neurological disorder and no deaths in prolonged febrile convulsions, idiopathic and unclassified CSE.

have reported higher mortality in individuals with prolonged status epilepticus (>60 min), continuous status epilepticus (compared with intermittent) and higher age, but this observation was valid only in adults and not for the paediatric population (Towne *et al.*, 1994; DeLorenzo *et al.*, 1999; Waterhouse *et al.*, 1999). Also, none of the previously reported predictors of short-term mortality following CSE in children, such as acute symptomatic cause of CSE, young age at onset, longer duration of CSE and focal-onset of CSE, were independently associated with mortality beyond 30 days in our cohort (Raspall-Chaure *et al.*, 2006; Sadarangani *et al.*, 2008). The observed differences in our study and other reported hospital-based studies may at least in part be related to the inclusion of more severe cases in hospital-based studies. The frequency of CSE and medication non-compliance may also potentially increase overall mortality. STEPSOUT is an ongoing study and the surviving cohort members are currently being recruited to determine the neurological, neuroimaging, cognitive and behavioural outcomes. The details on medication compliance, epilepsy control and frequency of CSE during follow-up are not available on all cohort members and we were not therefore able to adjust for these factors in our modelling.

We report the cause(s) of death in our cohort as stated on their death certificates. Most deaths within 30 days of an episode of CSE were as a consequence of complications of the underlying cause, such as acute bacterial meningitis or a progressive neurological disorder. Even among the 30-day survivors, the majority of deaths seem to have been associated with complications of their underlying brain disorder, rather than as a direct consequence of CSE. Only four deaths were seizure related; three as a result of CSE and one as a result of intractable seizures. There were no sudden unexpected deaths in epilepsy (SUDEP) or accidental

deaths. This is in contrast to the observation by Aicardi and Chevrie (1970), who reported that about half the deaths in their cohort with CSE were seizure related. There are several possible explanations for this observed difference. The first was that the Aicardi study (1970) was hospital based, and CSE was defined as continued seizure activity lasting at least 60 min rather than the 30 min used in our study. Thus, the children in the Aicardi (1970) study may reflect children with more severe conditions compared with our cohort. It is also possible that improvements in acute management of CSE in children in recent years may explain reduced risk of death as a direct consequence of CSE. Another explanation may be inaccuracies in the cause of death as stated on the death certificates as only 3 out of 23 in our study had autopsies, and the stated cause of death on certificates may not reflect circumstances surrounding death (Sillanpaa and Shinnar, 2010). It is possible that the actual cause of death may be due to seizure activity although not listed as such, e.g. unobserved seizure activity may lead to aspiration and subsequent respiratory failure.

As the main predictor of mortality is presence of pre-existing clinically significant neurological impairment at the time of CSE, it becomes important to ask whether CSE itself has any additional impact on subsequent mortality. There are no reported paediatric studies designed to address the independent influence of CSE on long-term mortality. Ideally, a direct comparison of the mortality in children with a pre-existing significant neurological disorder and no CSE, with a similar population of children with CSE, or mortality between idiopathic epilepsy without CSE and with CSE may help to determine the additional impact of CSE on mortality. However, even such an approach may not provide a satisfactory answer to this important question as the outcome may still be

Table 4 Clinical characteristics and cause of death in the deceased

Case	Age at CSE (years)	Age at death (years)	Diagnostic category of CSE	Cause of death (as stated on death certificate)

1[a]	1.2	1.2	Acute symptomatic	I (a) Brainstem herniation
				  (b) Cerebral oedema
				  (c) Pneumococcal meningitis

2[a]	2.1	2.1	Acute symptomatic	I (a) Increased intracranial pressure, coning (b) Meningococcal meningitis

3[a]	1.0	1.0	Acute symptomatic	I (a) Respiratory arrest
				  (b) Pneumococcal meningitis
				II Cerebral palsy, ventriculo-peritoneal shunt for hydrocephalus,
				   intraventricular haemorrhage at birth

4[a]	5.6	5.6	Remote symptomatic	I (a) Bronchopneumonia
				  (b) Intractable epilepsy
				  (c) West syndrome
				II Global developmental delay

5[a]	5.1	5.1	Remote symptomatic	I (a) Acute encephalopathy (b) Glutaric aciduria type I
6[a]	0.4	0.4	Remote symptomatic	I (a) Brain infarction (b) Congenital lactic acidosis
7[a]	0.5	0.5	Remote symptomatic	I (a) Progressive neurodegenerative disorder (b) Congenital mitochondrial disorder
8[b]	3.7	8.4	Acute symptomatic	I (a) Acute brain swelling/haemorrhagic infarction (b) Status epilepticus II Influenza A infection
9[b]	3.0	9.2	Cryptogenic	I (a) Sudden cardiac death (b) Acute lymphocytic myocarditis II Epilepsy
10	9.5	17.0	Cryptogenic	I (a) Septic shock with multiple organ failure (b) Community acquired pneumonia II Epilepsy

11	3.2	9.6	Cryptogenic	I (a) Acute cardiorespiratory failure
				  (b) Status epilepticus
				  (c) Dravet syndrome

12	5.2	8.5	Remote symptomatic	I (a) Lower respiratory tract infection (b) Intractable seizure disorder II Gastro oesophageal reflux
13	12.2	16.3	Remote symptomatic	I (a) Pneumonia (b) Cerebral palsy, spastic quadriplegia, epilepsy II Gastro oesophageal reflux with gastrostomy
14[b]	7.8	13.1	Remote symptomatic	I (a) Small bowel infarction (b) Volvulus II Cerebral palsy
15	1.5	7.0	Remote symptomatic	I (a) Cytochrome C oxidase deficiency
16	2.7	4.2	Remote symptomatic	I (a) Neurodegenerative disorder of unknown aetiology

17	13.4	13.5	Remote symptomatic	I (a) Status epilepticus
				  (b) Degenerative brain disease
				  (c) Mitochondrial encephalopathy

18	0.6	1.2	Remote symptomatic	I (a) Respiratory failure II Neurodegenerative disorder
19	0.7	1.1	Remote symptomatic	I (a) Congenital denervating neurological condition
20	11.2	16.8	Remote symptomatic	I (a) Bronchopneumonia II Cerebral palsy
21	2.6	3.0	Remote symptomatic	I (a) Severe pyridoxine deficiency (b) Severe epilepsy
22	1.0	6.9	Remote symptomatic	I (a) Ileus (b) Severe complex neurological disability
23	2.3	4.2	Remote symptomatic	I (a) Intractable seizures II Global developmental delay

a Deaths within 30 days of CSE.
b Had post-mortem examination.

confounded by the severity of the underlying structural/functional brain disorder and CSE itself could be a marker of the severity.

An indirect way of analysing the attributive role of CSE on mortality could be by comparing the mortality in idiopathic CSE in our cohort with the reported mortality in children with idiopathic epilepsy, and mortality in children with neurological impairments in our cohort with that of remote symptomatic epilepsy and cerebral palsy as these are the main groups that make up the subcategory

of children with pre-existing neurological problem in our cohort. There were no deaths in children who had idiopathic CSE in our cohort (SMR 0, 95% CI 0.0–3.68), an observation similar to the low mortality reported in children with idiopathic epilepsy (Harvey et al., 1993; Callenbach et al., 2001; Camfield et al., 2002; Berg et al., 2004; Geerts et al., 2010; Sillanpaa and Shinnar, 2010). The SMR for children with significant neurological impairment prior to their episode of CSE in our study was 91.4 (95% CI 53.2–146.3). In comparison, reported SMRs in children with symptomatic epilepsies range between 22.9 (95% CI 7.9–37.9) and 49.7 (95% CI 31.7–77.9) (Harvey et al., 1993; Callenbach et al., 2001; Berg et al., 2004; Geerts et al., 2010). The mortality in our cohort with significant neurological impairment prior to CSE appears to be higher than that reported for remote symptomatic epilepsy. However, children classified as having remote symptomatic epilepsy by definition do not necessarily have major neurological impairments and therefore the comparison with our group is not very robust (Engel, 2001). The mortality in our cohort is comparable with the reported mortality in children with cerebral palsy, a cohort likely to have similar neurological impairments (SMR 36.4 for mild and 102.8 for severe cerebral palsy, 95% CI not provided); however, a significant proportion of children with severe cerebral palsy probably had epilepsy and some also experienced episodes of CSE (Strauss et al., 1999). All these comparisons need to be interpreted with caution, as they do not take into consideration the heterogeneity of the study populations, the severity of underlying conditions in different cohorts and the unreported possible confounders affecting the outcome.

Long-term follow-up studies have reported no significant difference in mortality in children with epilepsy with or without status epilepticus (Sillanpaa and Shinnar, 2002; Stroink et al., 2007). Although a history of prior CSE was associated with increased long-term mortality on univariable analysis in some studies, this was no longer significant after adjusting for other clinical factors, and the underlying diagnosis was the major predictor of mortality (Callenbach et al., 2001; Camfield et al., 2002; Sillanpaa and Shinnar, 2002, 2010; Berg et al., 2004a, b).

The available data therefore suggest that CSE does not substantially increase the risk of death in neurologically normal children who survive the acute episode of CSE, and any impact it may have on increasing long-term mortality is seen primarily in children with significant underlying brain disorder. This, however, needs confirmation from studies designed to investigate the additional impact of CSE on mortality without being confounded by severity of underlying brain disorder, and a possible approach could be by comparing the mortality associated with short seizures against that with CSE in children without an identifiable underlying aetiology (e.g. febrile seizures, idiopathic epilepsy). One such study done in adult population showed a non-significant 2.4-fold increased risk of death at 10 years in incident idiopathic/cryptogenic CSE compared with short seizures (adjusted relative risk 2.4, 95% CI 0.9–6.3) (Logroscino et al., 2008). However, the study was limited by a small sample size, and the increased risk was restricted to the elderly and those who later developed epilepsy.

Our study is the largest prospective paediatric population-based cohort of CSE in resource-rich countries. Despite this, it is possible that lack of statistical significance for some of the clinical and demographic factors could be due to our modest sample size. As is inevitable in follow-up studies, there will be some degree of attrition but our 9% attrition is within the acceptable range for follow-up cohort studies (Fewtrell et al., 2008). Furthermore, the children who were lost to follow-up were similar to those for whom we had follow-up data suggesting that our results are representative of the entire CSE cohort. This study, from a resource-rich country, may well not reflect the longer term mortality in a resource-poor setting where it is already clear that the mortality within 3 years of an episode of CSE is substantially higher (Sadarangani et al., 2008).

In summary, our study provides novel information that will be useful for prognostication. There is a substantially increased risk for death within 8 years after CSE with having pre-existing clinically significant neurological disorder at the time of CSE being the major predictor. The risk of death is not increased in children with prolonged febrile convulsions and idiopathic CSE, and in those with acute symptomatic aetiology who survive the acute episode of CSE. Most deaths during follow-up occur as a complication of underlying brain disorder rather than seizures themselves. In addition, the study has generated the hypothesis that there is minimal additional impact of CSE itself on mortality. Case–control studies specifically designed to investigate this hypothesis are now required. Although it may be feasible to detect a significant difference in mortality among those with and without CSE, the challenge is identifying an appropriate control population. As CSE is associated with increased morbidity as well as mortality, research into morbidity following CSE in childhood is needed.

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