CURRENT TOPIC

Do seizures damage the brain? The epidemiological evidence

Christopher M Verity

Do seizures damage the brain? If they do, how often does it happen? The answers are very dependent on the type of research that is used to investigate the questions. Evidence has come from two areas of study that are of particular interest to paediatricians: the outlook for children who have febrile convulsions, and the prognosis after status epilepticus (in this paper febrile convulsions lasting longer than 30 minutes are called lengthy febrile convulsions and are considered separately from status epilepticus). When considering the outcome after seizures it is important to take account of the different types of study that have provided the evidence in children.

Know your study—selected groups or population based?
The advantage of studying a selected group of patients is that each individual can be carefully evaluated, perhaps using the latest imaging or neurophysiological techniques. The disadvantage is that patients who attend specialised clinics or hospitals tend to have relatively severe seizure problems and a worse outlook. By studying unselected groups of children or adults, population based studies have given a more optimistic view of outcome. This paper will refer particularly to three large population based studies:

- The National Collaborative Perinatal Project (NCPP) which enrolled approximately 54 000 pregnant American women between 1959 and 1966 and followed up their children until 7 years of age.1–3
- The system of medical records linkage of the Rochester Epidemiology Project which was used to identify residents of Rochester, Minnesota, USA, who had seizures.4–6
- The Child Health and Education Study (CHES), a birth cohort study, which enrolled over 16 000 neonatal survivors born in the United Kingdom in one week in April 1970 and followed them until 10 years of age.7–9

Outcome after febrile convulsions

The controversy
In 1971 Taylor and Ounsted10 wrote: “We think that the convulsive hypoxia sustained during prolonged febrile convulsions causes the death of vulnerable neurones in the cerebellum, the thalamus, and in mesial temporal structures.” However, in 1991 Robinson11 referred to the “generally excellent prognosis” for children with febrile convulsions. Investigators have reached very different conclusions about the harmful effects of febrile convulsions (see reviews12–16).

The definition of febrile convulsions
Some workers have included seizures that occur when children are febrile because of an underlying meningitis or encephalitis (Wallace,16 Stephenson”). However, it has become generally accepted that seizures that are known to be symptomatic of an underlying infection should not be called febrile convulsions.18 19 The Commission on Epidemiology and Prognosis of the International League Against Epilepsy (1993)20 agreed on the following definition:

“... an epileptic seizure occurring in childhood after age 1 month, associated with a febrile illness not caused by an infection of the CNS, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures”.

Simple versus complex febrile convulsions
In the American NCPP, complex febrile convulsions (seizures) were defined as those that had one or more of the following: (1) duration more than 15 minutes; (2) recurrence within 24 hours; (3) focal features. Febrile convulsions that did not have complex features were simple. Other studies have adopted very similar definitions.5–9 21–23

Studies of selected groups
Deaths: necropsy studies
In 1950 Ekholm and Niemineva reported a mortality rate of 11% in a group of children in hospital with “infection convulsions.”24 Fowler25 and Meldrum26 described neuronal necrosis in the cerebral cortex, the hippocampi, and the cerebellum of children who died after prolonged “febrile convulsions.” These necropsy studies were of extreme cases that were not typical of the majority of febrile convulsions (see below).

The cerebrospinal fluid of patients with febrile convulsions
Simpson et al found raised cerebrospinal fluid (CSF) lactate concentrations or lactate/
pyruvate ratios in some children with febrile convulsions,27 28 suggesting cerebral hypoxia. Other workers have not found evidence of metabolic disturbance in the CSF of children with febrile convulsions.29–31

AFEBRILE SEIZURES/EPILEPSY AFTER FEBRILE CONVULSIONS

Incidence
Wallace reviewed the rates of subsequent afebrile seizures and/or epilepsy (defined as “recurrent afebrile seizures”) in hospital based series and found that it varied from 7% to 40%.16

Retrospective study of patients with temporal lobe epilepsy
Falconer et al studied the temporal lobes removed from 100 adults because of refractory temporal lobe epilepsy.32 About half of the patients had “mesial temporal sclerosis” of the temporal lobe which varied from loss of nerve cells in the Sommer (H1) sector of the hippocampus to wider involvement of the temporal lobe; in 40% of these patients there was a history of “infantile convulsions” and the suggestion was therefore made that infantile convulsions cause temporal lobe damage. The association between mesial temporal sclerosis and a history of childhood febrile convulsions has subsequently been reported by many investigators, the more recent reports being based on magnetic resonance imaging (MRI) or functional imaging.10 33–36 Kuks et al pointed out that this association does not prove a causal relation.37 In their study 64% of the patients with MRI evidence of hippocampal volume loss gave no history of febrile convulsions, suggesting that if childhood febrile convulsions cause some cases of hippocampal sclerosis this is not the only mechanism. Possibly pre-existing minor cerebral abnormalities, such as focal cortical microdysgenesis, predispose both to complex febrile convulsions and to later epilepsy.11 38

Case report
Figure 1 is the MRI brain scan of an 8 year old girl with refractory complex partial (temporal lobe onset) seizures. It shows that the left hippocampus is smaller than the right. In the first year of life the girl had a febrile convolution which lasted for about half an hour and which particularly involved the right arm. She later developed afebrile complex partial seizures, some of which were secondarily generalised. The arrow marks the left hippocampus, which is smaller than the right. For further details see text.

Known infection of the central nervous system were included in this study. Aicardi and Chevrie excluded children with infection of the central nervous system but nevertheless outcome was poor for many in their series—they reported on 402 children with febrile convulsions who were in hospital or seen as outpatients; 37 had neurological sequelae, including 24 with hemiplegia.40

Subtle signs of neurological dysfunction can be missed: Schiotz-Christensen41 studied 14 pairs of monozygous twins discordant for febrile convulsions; there was an increased incidence of “soft signs” and behaviour disturbance in the twins who had experienced a febrile convolution—these may have preceded the convulsions.

INTELLECTUAL OUTCOME
After hospital admission or attendance with febrile convulsions, mental retardation was found at follow up in 22% by Lennox,42 13.4% by Aicardi and Chevrie,43 and 8% by Wallace and Cull.44 Schiotz-Christensen and Bruhn studied 14 monozygous twin pairs and showed significant intellectual impairments in those who had suffered with febrile convulsions, although the deficits were small.45

Population based studies of outcome after febrile convulsions

DEATHS
Two large population based studies found no deaths that were directly attributable to febrile convulsions (Nelson and Ellenberg,7 Verity and Golding7).
Some children had febrile convulsions with more than one complex feature. In the British CHES cohort, the rate of epilepsy in the cohort children who did not have febrile convulsions was 3.7/1000 (approximately 0.4%). In the cohort there were 382 previously normal children who had febrile convulsions. The table shows that the majority of these children (287) had simple febrile convulsions and in them the risk of subsequent epilepsy (recurrent afebrile seizures) was only slightly increased (1%). The risk was greater for the minority who had febrile convulsions that were complex (6%).

The corresponding American study, the NCPP, reported very similar results. By 7 years of age the rate of spontaneous epilepsy, not preceded by febrile convulsions, was 0.5%. After “pure” febrile convulsions, epilepsy developed in 1.5%, while after complex febrile convulsions it developed in 4%.

Outcome after different types of complex febrile convulsions
Table 1 shows that in the British CHES cohort the rate of epilepsy depended on the type of preceding complex febrile convulsion: 4% after multiple, 6% after prolonged, and 29% after febrile convulsions with focal features. There was overlap—febrile convulsions that were focal tended to be prolonged as well. Similarly, the American NCPP reported that when the first convulsion had prolonged, multiple, or focal features epilepsy developed in (approximately) 3%, 4%, and 7% respectively.

Annegers et al found that the risk of “unprovoked seizures” ranged from 2.4% among those that had simple febrile convulsions to 8% for those with a single complex feature, 17–22% with two complex features, and 49% with all three complex features.

Partial versus generalised epilepsy after febrile convulsions
The study of selected groups of children (see above) has led to the concern that prolonged febrile convulsions cause damage to the temporal lobe leading to complex partial epilepsy. Population based studies have provided evidence about the type of afebrile seizure that occurs in children who have had febrile convulsions. Some of the relevant findings are summarised below.

Only a very small proportion of children with prolonged febrile convulsions in the British CHES cohort developed complex partial epilepsy. Of the 382 normal children who had febrile convulsions, 32 had convulsions that were “prolonged” (longer than 15 minutes). Just three of these children, two of whom had convulsions with focal features, later had one or more afebrile complex partial seizures.

In a population based study in Nova Scotia, Camfield et al found that prolonged febrile convulsions rarely preceded intractable complex partial seizures. Febrile convulsions most often preceded generalised tonic-clonic afebrile seizures.

The CHES cohort did show an association between the occurrence of complex febrile convulsions (particularly those with focal features) and later afebrile complex partial seizures. Febrile convulsions that were focal tended to be prolonged. In the study there were 382 previously normal children who had febrile convulsions and 13 developed one or more afebrile seizures. Nine of the 13 had complex febrile convulsions and six of the nine developed afebrile complex partial seizures.

Annegers et al found in the Rochester study that febrile convulsions that were focal, repeated, or prolonged were strongly associated with subsequent partial afebrile seizures. They thought that the association did not prove that complex febrile convulsions cause later epilepsy. They suggested an alternative explanation—that the tendency to have complex febrile convulsions reflects pre-existing brain disease that is also responsible for the subsequent development of partial epilepsy.

If febrile convulsions cause afebrile complex partial seizures it would be expected that those children who had febrile convulsions would subsequently have a relatively greater proportion of afebrile complex partial seizures than those who did not have febrile convulsions. The CHES cohort data were used to investigate this. The number of children with afebrile seizures in the 14 278 children who did not have febrile convulsions was used to predict the number with afebrile tonic-clonic seizures and afebrile complex partial seizures that would be expected in the 398 children who did have febrile convulsions. There was no excess of complex partial seizures in the febrile convulsion group. Lee et al reported similar findings in Denmark, both studies suggesting that febrile convulsions do not contribute appreciably to the occurrence of complex partial seizures in the general population.

Recurrence of febrile convulsions
There are reports that recurrent episodes of febrile convulsions are associated with an increased risk of later epilepsy. If seizures damage the brain it might be expected that each convulsion would predispose to further convulsions. However, the sequence: brief first febrile convulsion followed by prolonged febrile recurrence followed by epilepsy was not seen once among 1706 children with febrile convulsions in the American NCPP. In the CHES cohort only four of the 382 previously normal children with febrile convulsions had a first simple febrile convulsion followed by a

Table 1  Data from the child health and education study, a national cohort study of children born in the United Kingdom in April 1970. The table shows the number of previously normal children with febrile convulsions who developed epilepsy in the first 10 years of life

<table>
<thead>
<tr>
<th>Type of febrile convulsion</th>
<th>No of children with febrile convulsions</th>
<th>No (%) of children who developed epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>287</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Complex ¶</td>
<td>95</td>
<td>6 (6)*</td>
</tr>
<tr>
<td>Multiple</td>
<td>55</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Prolonged</td>
<td>32</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Focal</td>
<td>17</td>
<td>5 (29)†</td>
</tr>
</tbody>
</table>

¶ Some children had febrile convulsions with more than one complex feature. *p<0.05, †p<0.001 of children who had simple febrile convulsions.
complex febrile recurrence and then by an afebrile seizure: also the proportion of first febrile convulsions that was complex was 20% whereas the proportion of recurrent febrile convulsions that was complex was lower—17%. Thus in the American and the British studies the evidence was against the hypothesis that there was progressive “damage” leading to more severe attacks.

NEUROLOGICAL IMPAIRMENT
Population based studies report a much better outcome than hospital based studies. No child in the NCPP5 developed a persisting hemiplegia or other motor deficit during or immediately after an asymptomatic febrile convulsion.1

INTELLECTUAL OUTCOME
There is a contrast between the hospital based studies and the population based studies. Ellenberg and Nelson tested 431 sibling pairs who were discordant for febrile convulsions in the NCPP and found that at 7 years of age children who were normal before any febrile convulsion did not differ in intelligence quotient from their normal seizure-free siblings.1 Children who were suspect or abnormal before the first febrile convulsion scored significantly lower IQs than their siblings. Neither recurrent seizures nor those lasting longer than 30 minutes were associated with IQ deficit. Population based studies in Britain5 51 found little difference in intellectual or behavioural outcome between previously normal children who had febrile convulsions and their peers.

OUTCOME AFTER FEBRILE CONVULSIONS—
CONCLUSIONS
Investigators who report a poor outcome have studied selected groups of children attending specialised hospitals or clinics. Sometimes they have included children who have suffered from convulsions that complicate meningitis or encephalitis. Some have included children who were known to be developmentally or neurologically abnormal before they had their first febrile convulsion. In contrast population based studies that have studied a less selected group of children give a much more positive view. Such studies show that:
• Most children that have febrile convulsions are normal individuals who have simple febrile convulsions, the majority of which do not recur;
• In children with simple febrile convulsions there is little evidence of long term effects on behaviour or intelligence and the increased risk of later epilepsy is slight;
• The minority of children have complex febrile convulsions and for most of them the outlook is good; however, within this group there are a few children who have an increased risk of later epilepsy, the risk being greatest for those who have febrile convulsions with focal features, which tend to be prolonged.

Certainly there is evidence of an association between temporal lobe onset seizures and a history of previous febrile convulsions. Do febrile convulsions cause temporal lobe damage and lead to afebrile complex partial seizures of temporal lobe onset? Alternatively, does the association result from the fact that some children have a predisposition to partial seizures which becomes evident for the first time as a febrile convulsion? At present it is difficult to be certain about the answers. The population based studies provide evidence that if febrile convulsions cause hippocampal damage this happens rarely.

The outcome after lengthy febrile convulsions and status epilepticus
THE CONTROVERSY
In 1970 Aicardi and Chevrie wrote: “the prognosis of children’s status epilepticus is grave, mental and neurological residua or both being present in at least 57% of our patients”.54 In 1989 Maytal et al reported low morbidity and mortality of status epilepticus in children and they concluded that the outcome of status epilepticus is primarily a function of the underlying cause.55

Case report
Figure 2 is the MRI brain scan of a 4 year old boy who presented with delayed development. Subsequently he had seizures and episodes of status epilepticus. After one such episode brain scans showed extensive changes in the cerebral hemispheres and these progressed to generalised atrophy, as can be seen in fig 2. CSF lactate concentrations were raised, suggesting that the boy had a mitochondrial cytopathy and this was confirmed by analysing muscle enzymes in a biopsy taken immediately after death. It was concluded that the cerebral atrophy was caused by the metabolic disorder rather than by the prolonged seizures. If no diagnosis had been made, the progressive atrophy seen on the scans might have been attributed to the seizures.

DEFINITIONS
Status epilepticus
The minimum length of time required for a seizure to be regarded as an episode of status epilepticus has become shorter with time.54 56 57 Aicardi and Chevrie54 and Oxbury and Whitty58 regarded one hour as the minimum. Now 30 minutes is more generally required.54 56 57

The guidelines published by the International League Against Epilepsy20 defined status epilepticus as:
“a single epileptic seizure of > 30 min duration or a series of epileptic seizures during which function is not regained between ictal events in a > 30 min period”.

Status epilepticus associated with fever
Maytal and Shinnar used the term “febrile status epilepticus” to describe prolonged febrile convulsions.66 However, some children with status epilepticus are febrile and yet their seizures are not febrile convulsions, according to currently accepted definitions. Also the fever is sometimes a direct result of the seizure activity and does not persist after the seizures.

To clarify the situation I suggest that the following definitions are used:
Status epilepticus associated with fever—status epilepticus preceded by hyperthermia or (if the temperature was not taken before the convulsion) when fever is present at the initial medical examination and persists. The term includes two main groups:

(a) Lengthy febrile convulsions—febrile convulsions that last longer than 30 minutes (Nelson and Ellenberg were perhaps the first to use the term in this way).3

(b) Acute symptomatic febrile status epilepticus—an episode of status epilepticus which is preceded and accompanied by fever and which is concurrent with and considered to be the consequence of an acute disorder of the central nervous system (usually an intracranial infection).

Outcome after lengthy febrile convulsions
The outcome after febrile convulsions has been reviewed above. This section deals with the extreme cases—those that have febrile convulsions lasting longer than 30 minutes. These attacks occur quite rarely (see below) but in the context of a discussion about possible damage caused by seizures they are worth considering separately.

STUDIES OF SELECTED GROUPS
Aicardi and Chevrie retrospectively reviewed 402 patients with febrile convulsions, hospital inpatients or seen as outpatients.4 They identified 118 who had convulsions lasting 30 minutes or longer and the outcome was not good. Epilepsy occurred in 53 children (45%), mental retardation in 35 (30%), and there were other neurological sequelae in 24 (20%).

A more recent paper by Maytal and Shinnar was also hospital based, but gave a much more optimistic view.5 As part of a larger study of childhood status epilepticus, 44 children with febrile convulsions lasting more than 30 minutes were identified (30 prospectively and 14 retrospectively). No child died or developed new neurological deficits following the seizures. The risk of subsequent afebrile seizures was only increased in those children with previous neurological abnormality. The conclusion was that the morbidity and mortality of febrile convulsions lasting more than 30 minutes was low.

Maytal and Shinnar60 compared their study with that of Viani et al63 who found much higher rates of afebrile seizures after “infantile febrile status epilepticus”. The latter study was a retrospective case note review of patients who were already being followed up in an epilepsy clinic. It included children with previous afebrile seizures and previous neurological abnormalities, and those who were febrile because of underlying meningitis or encephalitis. It was therefore not surprising that these investigators reported a worse outcome.

Van Esch et al reported neurological sequelae in 12 out of 57 children with “febrile status epilepticus”—nine developed speech deficits and three severe neurological sequelae and epilepsy.64 The 57 children were said to be without previous neurological deficits or seizures, but they were a selected group, having all been admitted to hospital, and were identified retrospectively.

POPULATION BASED STUDIES
Epilepsy
In the American NCPP there were 74 children who had a first febrile convulsion lasting 30 minutes or more; Nelson and Ellenberg called these “lengthy febrile seizures”.3 Of these children, just three (4.1%) became epileptic by 7 years of age. The increase in risk of subsequent epilepsy in those with first febrile convulsions lasting half an hour or more was higher than in those who had uncomplicated initial febrile convulsions, but did not reach statistical significance.

In the British CHES cohort there were 398 children who had febrile convulsions (16 were known to have preceding neurodevelopmental abnormalities).62 Nineteen (4.8%) had lengthy febrile convulsions. There were no deaths and no further lengthy febrile convulsions. However, the risk of later afebrile seizures was significantly greater than in those children that had febrile convulsions lasting less than 30 minutes. Annegers et al reported similar findings.2

Intellectual outcome
Among the children with febrile convulsions in the NCPP there were 431 sibling pairs who were discordant for febrile convulsions and were tested at 7 years of age.1 Twenty seven of the children had a febrile convulsion lasting 30 minutes or more. The mean full scale IQ in these children was not significantly different from their control siblings (this was also true of the 14 children who had febrile convulsions lasting an hour or longer).

In the British CHES cohort62 there were 19 children with lengthy febrile convulsions. One child became hyperpyrexial after being placed in a hot bath, in the parents’ mistaken belief that this was the appropriate management for febrile convulsions. He was the only child in whom permanent new neurological signs were
documented after a lengthy febrile convolution and he was below normal on tests at 10 years of age. Except for this one atypical case there was no evidence of poor intellectual outcome in those who had been normal before the lengthy febrile convulsions.

Outcome after status epilepticus in children

STUDIES OF SELECTED GROUPS

Most of the published series on outcome after status epilepticus have been hospital based. The retrospective studies have reported the worst outcomes. The prospective studies have reported better outcomes.

In a major retrospective review of status epilepticus in children, Aicardi and Chevrie reported on the outcome of 239 patients under 15 years of age, either hospital inpatients or seen as outpatients. This study only included convulsive status lasting more than one hour. The outcome was reported as “grave, mental or neurological residua or both being reported in at least 57% of our patients”. Death occurred in 11% (attributed to the seizures themselves in about half the cases), 37% developed permanent neurological signs, 48% were mentally retarded. The children had very severe seizures—the authors stated that most of their patients were “treated after several hours”.

A more recent study of status epilepticus in children was hospital based and children were identified both prospectively and retrospectively (Maytal et al55). The authors reported a much better outcome than Aicardi and Chevrie. The minimum time required to fulfill the definition of status epilepticus was 30 minutes. The 193 children studied were a heterogeneous group, ranging in age from 1 month to 18 years (mean 5 years). The status epilepticus was described as idiopathic in 46 cases, remote symptomatic in 45, febrile in 46, acute symptomatic in 45, and progressive neurological in 11. The majority of seizures were “generalised”. Seven children died within three months of having the seizure. New neurological deficits were found in 17 (9.1%) of the 186 survivors. All of the deaths and 15 of the 17 sequelae occurred in the 56 children with acute or progressive neurological insults. Only two of the 137 children with other causes sustained any new deficits. The authors concluded that in the absence of an acute neurological insult or progressive neurological disorder the morbidity of aggressively treated status epilepticus in children is low. It appeared that the outcome of status epilepticus is primarily a function of the underlying cause.

The authors thought that the difference in patient selection was the main explanation for differences in outcome between their series and that of Aicardi and Chevrie.56

A POPULATION BASED STUDY

In the CHES study information was available for 14 676 children who had been followed up for the first 10 years of life. There were 84 children who had one or more afebrile seizures and 18 (21%) of them had one or more episodes of status epilepticus (16 had episodes of convulsive status epilepticus and two non-convulsive status epilepticus). Two children died—one quickly as a result of the underlying cause of the status, haemorrhage from a haemangiendothelioma. The other presented with an illness diagnosed as an encephalitis and died several years later of bronchopneumonia. Thus neither death was due to the status epilepticus. Of the 16 survivors, eight were normal on tests of development at 5 or 10 years of age, and outcome measures were not available for one. The remaining seven were either in special schools or were below normal on testing at 10 years of age—in all of these there was either an underlying neurological abnormality or concern about development before the episode of status epilepticus.

The conclusion from this population based study was similar to that reached by Maytal et al55—that the outcome after status epilepticus is determined by more by the underlying neurological problem than by the status epilepticus itself.

Conclusions—lengthy febrile convulsions and status epilepticus

Population based studies report better outcome than hospital based studies because they do not select the more severely affected cases. However, this does not invalidate research that is hospital based. There is experimental and clinical evidence that prolonged seizure activity can damage susceptible neurones. But if such damage occurs, how often does it happen? The population based studies suggest that:

- Damage occurs much less frequently than is indicated by the study of selected groups of children in hospital;
- The outcome is dependent more on the underlying cause for the seizures than the seizures per se.

Other recent studies (Maytal and Shinnar57) reach similar conclusions, partly because they have relied less heavily on retrospective data and partly because they have reported the outcome for a less seriously ill group of children.

Although the population based studies quoted above suggest that brain damage occurs much less often than was previously reported, they do not justify a complacent approach to the management of prolonged seizures. The aim should be to terminate such seizures as quickly as possible, and the management of status epilepticus should still be regarded as a medical emergency. However, worried parents can be reassured by the epidemiological evidence that if seizures cause “brain damage” it happens rarely.

The papers reporting on children with febrile convulsions and epilepsy in the Child Health and Education Study were written with the active collaboration and support of Professor Jean Golding and Ms Rosemary Greenwood of the Institute of Child Health, University of Bristol, together with Professor Euan Ross of the Department of Community Paediatrics, King’s College Hospital, London. We thank the midwives, health visitors, general practitioners, medical records officers, and clinicians who provided essential information and also the children and their parents. Professor Neville Butler initiated the Child Health and Education Study, which was funded by the Medical Research Council, the Department of Health and Social Security and the Gertrude H Sergievsky Centre, Columbia University, New...
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