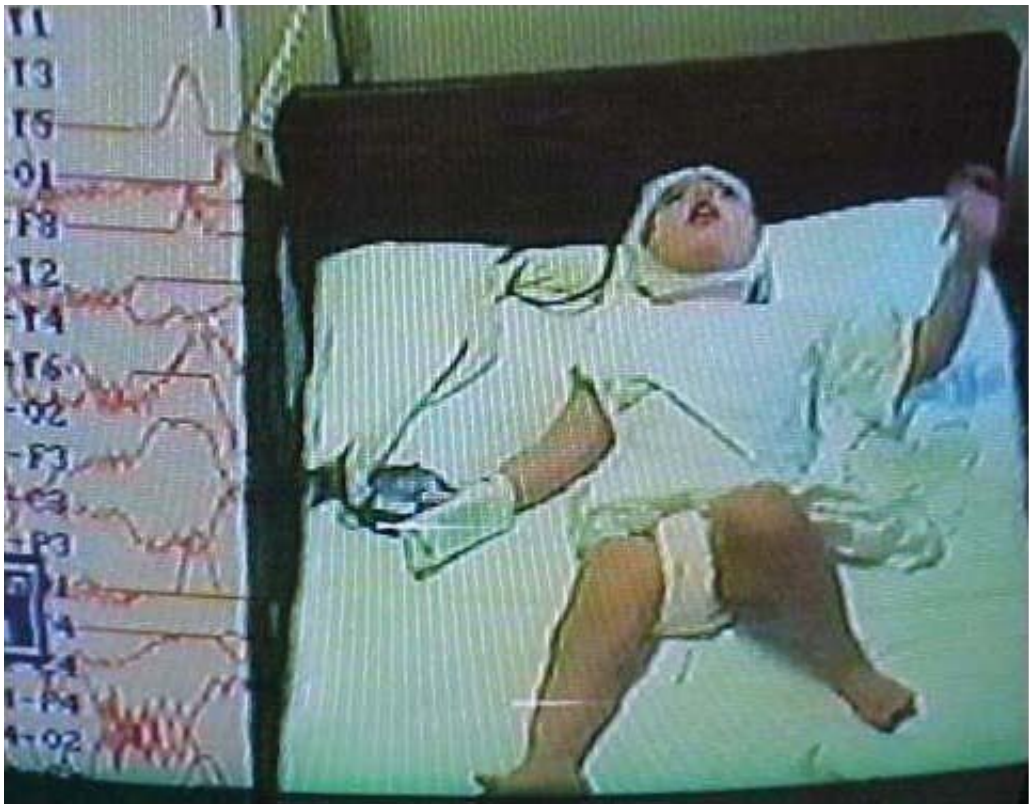

An 18-month-old-girl having a complex febrile seizure, recorded on video EEG.

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Febrile seizures are seizures that occur between the age of 3 months and 5 years, with a temperature of 38 °C or higher, and which are not the result of central nervous system infection or any metabolic imbalance. They are either simple (referred to as typical) or complex (atypical):

- A simple febrile seizure is a primary generalized, usually tonic-clonic attack, associated with fever, lasting no more than 15 min, and not recurring within a 24-h period.
- Complex febrile seizures, on the other hand, are more prolonged, focal, and/or recur within 24 hours (Baumann & Duffner 2000).

Between 2 and 5% of neurologically healthy infants and children experience at least one, usually simple, febrile seizure.

CLINICAL COURSE AND LONG-TERM PROGNOSIS

The risk of recurrence

The only definite risk associated with simple febrile seizures is recurrence. This occurs in 30% of those experiencing a first episode, in 50% after two or more episodes, and in 50% of infants less than 1 year of age (Baumann & Duffner 2000). Several factors affect this recurrence risk (Tables 1 and 2). In the Berg series, 347 children with a first febrile seizure were followed up for an average of 20 months. The predictors of recurrence were short duration of illness before the seizure, low body temperature at the time of seizure, a family history of febrile seizures, and

Febrile seizures in children

Table 1 Predictors of recurrence of febrile seizures: individual risk factors

RISK FACTOR	REFERENCE(S)
Age at 1st seizure	
‹ 18 months	Berg *et al*. (1992)
‹ 14 months	Knudsen (1985), Nelson & Ellenberg 1978)
Low body temperature at time of seizure	Berg *et al*. (1992), El Radhi 1998)
Positive family history of febrile seizures	Berg *et al*. (1992), Knudsen (1985)
Positive family history of epilepsy	Knudsen (1985), Rich *et al*. (1987)
Complex nature of febrile seizure	Knudsen (1985), Bessisso *et al*. (2001)
Short duration of illness/fever before seizure	Berg *et al*. (1992)
Attendance at day care	Knudsen (1985)
Low serum sodium levels	Hugen *et al*. (1995)
Male gender	Bessisso *et al*. (2001)

Table 2 Predictors of recurrence of febrile seizures: an additive model to predict risk

NUMBER OF RISK FACTORS PRESENT*	RECURRENCE RISK (KNUDSEN 1985; BERG *ET AL*. 1992; BERG & SHINNAR 1996B)
0	12%
1	25–36%
2	50–59%
3 or more	73–100%
Overall	30%

*risk factors in Table 1.

age at first seizure less than 18 months. Knudsen (1985) reported six 'additive' predictive factors for recurrence: complex nature of the febrile seizure, age less than 14 months, family history of febrile seizures, family history of epilepsy, attendance at day care, and developmental delay. The risk for an individual child ranged from 12% if none of these factors were present to 100% if all were present. Risk factors for febrile seizure recurrence in the study by Bessisso and colleagues (Bessisso *et al*. 2001) were male gender and having complex febrile seizures. El Radhi (1998) studied 132 children with their first febrile seizure, measured their body temperature at the onset of the seizure, and followed them for an average of 2 years. Children whose body temperature was 39 °C at the onset of the seizure were 2.5 times more likely to have multiple convulsions during the same illness (when their temperature rose above that which caused the initial convulsion) than those with a temperature less than 39 °C. These patients were also three times more likely to experience recurrent febrile convulsions in subsequent illnesses. Hugen and colleagues (Hugen *et al*. 1995) found an almost linear association between serum sodium levels and recurrent febrile convulsions – the lower the level, the higher the risk.

The risk of brain damage

There are no long-term adverse effects of having one or more simple febrile seizures. Specifically, recurrent simple febrile seizures do not damage the brain. Although a number of hospital-based studies reported deficits in speech, drawing, arithmetic, attention and intelligence in patients with febrile seizures, these were biased by referral patterns. Moreover, the findings have not been confirmed by population-based studies. Kolfen *et al*. (1998) compared 80 children 6–9 years old, with a history of febrile convulsions, with matched healthy controls. Of note is that the group with febrile seizures included children with prolonged febrile convulsions (18%) and some children with discrete neurological abnormalities (7%). Neuropsychological test results were no different between children with febrile seizures and their healthy controls. However, in children with prolonged febrile convulsions, non-verbal intelligence was significantly lower than in children with simple febrile seizures and controls. The population-based study in the UK comprehensively assessed 381 children with febrile convulsions (simple or complex) at 10 years of age and compared them with healthy children using measures of academic progress, intelligence and behaviour – there was no difference (Verity *et al*. 1998). A recent population-based study was conducted on 103 children with confirmed febrile seizures by 3 years and followed up until age 6 years. Compared with age-matched controls, there were no adverse effects on behaviour, scholastic performance or neurocognitive attention (Chang *et al*. 2000; Chang *et al*. 2001).

The risk of developing epilepsy

Although about 15% of children with epilepsy have had febrile seizures (Camfield *et al*. 1994), only 2–7% of children who experience febrile convulsions develop non-febrile seizure disorders and epilepsy later in life (Johnson *et al*. 1998). There are several predictors of epilepsy after febrile seizure (Tables 3 and 4). Complex febrile seizures, neurodevelopmental abnormalities, a family history of epilepsy, recurrent febrile seizures, and a short duration of fever before the initial febrile seizure were all associated with an increased risk of epilepsy in the study by Berg & Shinnar (1996a). However, in other studies multiple recurrences did not predict subsequent epilepsy (Camfield *et al*. 1994; Camfield & Camfield 1997). Verity & Golding (1991) demonstrated that a higher risk for later epilepsy occurs in patients with complex febrile seizures (6%), particularly focal febrile seizures (29%), as compared to simple febrile seizures (1%).

When febrile seizures are followed by non-febrile seizures, they are usually tonic–clonic in type as part of primary or secondary generalised epilepsy (Camfield *et al*. 1994). Choueiri *et al*. (2001) showed that 36% of patients with temporal lobe epilepsy had had prior febrile seizures, but only 6% of patients with primary generalized epilepsy had such a history.

It is likely that many patients who develop febrile status epilepticus develop neuronal injury and secondary epilepsy, often as a result of medial temporal sclerosis. Despite this, the above-mentioned increased risk for later epilepsy after febrile seizures is thought to be predominantly due to genetic predisposition and not due to structural damage to the nervous system caused by recurrent febrile seizures.

Genetic factors

Febrile seizures are often familial. Choueiri *et al*. (2001) showed that patients with febrile seizures were more likely to have a family history of fe-

Although about 15% of children with epilepsy have had febrile seizures, only 2–7% of children who experience febrile convulsions develop non-febrile seizure disorders and epilepsy later in life

Table 3 Predictors of subsequent epilepsy

RISK FACTOR	REFERENCE(S)
Complex febrile seizures	Nelson *et al*. (1978), Berg & Shinnar (1996a), Verity & Golding 1991
Neurodevelopmental abnormalities	Nelson *et al*. (1978), Berg & Shinnar (1996a)
Family history of epilepsy	Nelson *et al*. (1978), Berg & Shinnar (1996a)
Recurrent febrile seizures	Berg & Shinnar (1996a)
Short duration of fever before initial febrile seizure	Berg & Shinnar (1996a)

Table 4 Predictors of subsequent epilepsy and cognitive impairment

RISK FACTOR	RISK OF LATER EPILEPSY (NELSON *ET AL*. 1978; VERITY & GOLDING 1991; BERG & SHINNAR 1996a)	LATER COGNITIVE IMPAIRMENT (VERITY *ET AL*. 1998; CHANG *ET AL*. 2000, 2001)
None	1%	Similar to general population
Four or more febrile seizures	4%	
Complex febrile seizure (any type)	6%	
Complex febrile seizure (focal)	29%	Similar to general population
Fever < 1 h before febrile seizure	11%	irrespective of presence of risk factors*
Family history of epilepsy	18%	
Neurodevelopmental abnormality	33%	
Average	2–7%	

* The characteristics and risk factors of febrile convulsions including age at onset, presence or absence of complex febrile convulsions, recurrence rate of febrile convulsions, presence or absence of subsequent unprovoked seizures, prior use of anticonvulsants, and seizure free duration were not associated with any neurocognitive attention deficits in febrile convulsion patients.

Table 5 Identified gene loci of febrile seizures

GENE LOCUS	INHERITANCE	REFERENCE(S)
FEB1 on 8q13–21	Autosomal dominant	Wallace *et al*. (1996)
FEB2 on 19p13.3	Autosomal dominant	Johnson *et al*. (1998)
FEB4 on 5q14-q15	Autosomal dominant	Nakayama *et al*. (2000)

Table 6 Generalised epilepsy with febrile seizures plus syndromes

SYNDROME/GENE LOCUS	GENE PRODUCT	INHERITANCE	REFERENCE(S)
GEFS + 1 on 19q13 (SCN1B)	β1 subunit of the voltage-gated sodium channel	Autosomal dominant	Wallace *et al*. (1998)
GEFS + 2 on 2q23-q31 (SCN1A)	α subunit of the voltage-gated sodium channel	Autosomal dominant	Escayg *et al*. (2000)
GEFS + 3 on 5q31.1-q33.1 (GABRG2)	GABA(A) receptor γ2-subunit	Autosomal dominant	Baulac *et al*. (2001)

brile seizures (20%) than patients with epilepsy (1%), and less likely to have consanguineous parents (4% vs. 20%). These findings favour autosomal dominant, rather than autosomal recessive, inheritance of febrile seizures. Rich *et al*. (1987) performed complex segregation analysis on 467 nuclear families. Nearly dominant seizure susceptibility was found in families of probands with multiple febrile convulsions, while families of probands with single febrile convulsions followed a polygenic model of inheritance. Several febrile convulsions gene loci have been identified (Table 5).

Generalized epilepsy with febrile seizures plus (GEFS+) is an autosomal dominant syndrome of highly variable phenotype, with onset in early childhood and remission in mid-childhood (Table 6). It is characterized by multiple febrile seizures and by several types of afebrile generalized seizures. These include generalized tonic clonic, absence, atonic, myoclonic and myoclonic astatic seizures of variable severity. One type is GEFS+1, which has been linked to mutations in the gene SCN1B on 19q13 encoding the β1 subunit of the voltage-gated sodium channel (Wallace *et al*. 1998). GEFS+2 has linkage to the 2q23-q31 gene SCN1A encoding for the alpha subunit (Escayg *et al*. 2000). A K289M mutation in the GABA (A) receptor gamma 2-subunit gene has been reported in a family with GEFS+ phenotype and was identified as the GEFS+3 type (Baulac *et al*. 2001).

WORKUP OF A CHILD WITH FEBRILE SEIZURES

Lumbar puncture

This is recommended in all children younger than 12 months of age after their first febrile seizure to rule out meningitis. Especially important to consider is the child who has received prior antibiotics that might mask the clinical symptoms of meningitis. The presence of an identified source of fever like otitis media does *not* rule out meningitis. Seizure activity is the major sign of meningitis in about 15% of children of whom about one third have no other meningeal signs. A child between 12 and 18 months should also be considered for lumbar puncture because even at that age the clinical evidence of meningitis may be very subtle. For children above 18 months, a lumbar puncture is only needed if there are signs or symptoms of meningitis (such as neck stiffness), Kernig and Brudzinski signs, or if there is any suggestion of intracranial infection.

EEG

If the child presents with a first simple febrile seizure, and is otherwise healthy (neurologically), an EEG should not normally be performed (Provisional Committee on Quality Improvement 1996). It does not help predict the recurrence of febrile seizures, or epilepsy, even if it is abnormal (Alvarez *et al*. 1983).

Blood tests

These are not routinely recommended in the workup of a child with a first simple febrile seizure. Blood glucose should be determined only if the child has prolonged post ictal drowsiness (Provisional Committee on Quality Improvement 1996).

Neuroimaging

According to the American Academy of Paediatrics practice parameter, a CT brain scan or magnetic resonance imaging is not recommended in a child after a first simple febrile seizure (Provisional Committee on Quality Improvement 1996). There are no data to support brain imaging in such patients.

Complex febrile seizures

The workup of children with *complex* febrile seizures must be individualized, but often includes an EEG and brain imaging, particularly if the child is neurologically abnormal.

TREATMENT

After weighing the risks and benefits, no antiepileptic therapy – intermittently just during periods of fever, or long-term – is recommended for prophylaxis in children with one or more simple febrile seizures (Baumann & Duffner 2000). Parents should be counselled on how to handle any future seizure, and given emotional support. If the seizure lasts for more than 2–3 min, then acute treatment with intravenous or rectal diazepam may be required. Intravenous phenobarbitone or other agents, such as intravenous valproate or phenytoin, may be needed acutely in febrile status epilepticus. If the parents are very anxious, intermittent oral diazepam can be given during any future febrile illness to help prevent recurrence of febrile seizures (Baumann & Duffner 2000). In addition, antipyretics may comfort the child. Antiepileptic drugs (AEDs) may be considered for children with *complex* febrile seizures, but currently available data indicate that the risk of future epilepsy is not reduced.

Intermittent therapy during fever

Antipyretics

Although antipyretics may comfort the child during a febrile illness, they do not prevent recurrence of febrile seizures (Schnaiderman *et al*. 1993; Baumann & Duffner 2000). One explanation might be that, in many children, seizures occur at a somewhat low temperature and the antipyretic does not lower the temperature completely to normal. In addition, febrile seizures often occur as the temperature is rising before antipyretics have had a chance to exert their effects. Van Esch *et al*. (1995) compared paracetamol 10 mg/kg with ibuprofen 5 mg/kg in 70 randomized children. Although ibuprofen was more effective in reducing body temperature, no significant differences were found in seizure recurrence between the two groups.

Oral diazepam and other benzodiazepines

Uhari *et al*. (1995) randomized 180 children to diazepam and paracetamol, diazepam and placebo, paracetamol and placebo, or two kinds of placebo. Diazepam was given as an initial rectal dose, followed after 6 h by oral doses of 0.2 mg/kg tid for the first two days of a febrile illness (when body temperature was > 38.5 °C). The four groups were followed for 2 years and compliance was excellent. The low doses of paracetamol or diazepam, and their combination, were ineffective for febrile seizure prevention. On the other hand, in the study by Rosman *et al*. (1993), in which a higher dose of oral diazepam was used (0.33 mg/kg every 8 h during fever), there was reduction in the risk of recurrent febrile seizures of 44%. Intermittent oral nitrazepam, clobazam and clonazepam (0.1/kg/day) have also been shown to be effective in reducing the risk of recurrence of febrile seizures (Wallace 1988).

Rectal diazepam

This is usually used to stop ongoing seizures in hospital, or by parents at home. If used at home, parents are carefully instructed about the specific dose to be administered to the child. It has also been used as a prophylaxis to reduce recurrence at the time of febrile illness. In the study by Knudsen & Vestermark (1978), children were randomized to either rectal liquid diazepam (0.5 mg/kg every 12 h) during illness or daily phenobarbitone. Both treatments were equally effective – or ineffective because there was no placebo – and adverse effects were minimal. In the study by Lee *et al*. (1986), intermittent diazepam prophylaxis 0.5 mg/kg administered as a rectal suppository every 8 h for up to 48 h when the temperature exceeded 38.5 °C, was found to be as effective as continuous oral sodium valproate. Again, in this study there was no placebo group.

Long-term antiepileptic drug therapy

In a recent meta-analysis of 47 controlled trials it was found that phenobarbitone approximately halved the risk of recurrence of febrile seizures (relative risk 0.51, 95% CI 0.32 to 0.82) (Temkin

2001). Most trials showed benefit, provided the drug was given daily, with compliance monitored and therapeutic blood levels maintained. Bacon *et al*. (1981) compared phenobarbitone, phenytoin and placebo in infants less than 14 months of age – phenobarbitone reduced febrile seizure recurrence significantly, while phenytoin did not. Nor was carbamazepine as effective as phenobarbitone as an initial drug for the prevention of recurrent febrile convulsions (Anthony & Hawke 1983). Another meta-analysis of randomized, placebo-controlled, trials of prophylaxis for febrile seizures found that children receiving either phenobarbitone or valproate had significantly lower risks of recurrence than those on placebo (Rantala *et al*. 1997).

Adverse effects of antiepileptic drug therapy

Cognitive and behavioural adverse effects are mostly encountered with phenobarbitone. Available data suggest that 20% to 40% develop behavioural problems (hyperactivity, irritability, and sleep disorders) and a smaller proportion suffer from idiosyncratic reactions (Baumann & Duffner 2000). Wolf *et al*. (1981) compared phenobarbitone treated children with those receiving no therapy on various psychometric tests and no significant differences were found on any scale at the initial evaluation or at the 3-month follow-up. Farwell *et al*. (1990), however, documented a decline in intellectual ability of children on phenobarbitone who had on average a lower IQ by 7.03 points as compared with the placebo group after 2 years of treatment. After stopping the medication for 6 months, the IQ was still 5.2 points lower in the phenobarbitone group. A continuation of this study found that, 3–5 years later, the difference in IQ was non-significant. However, the phenobarbitone group scored significantly lower on the reading achievement standard score of the Wide Range Achievement Test (Schulzbacher *et al*. 1999).

The use of sodium valproate has been discouraged in the treatment of febrile seizures because of fears of life-threatening liver toxicity in infants and children. It is specifically not recommended up to 3 years of age (Baumann & Duffner 2000). Thrombocytopenia, pancreatitis and weight gain are other adverse effects.

In the study by Uhari *et al*. (1995), 39% of the children on intermittent oral diazepam (0.3 mg/kg) had moderately severe adverse effects of somnolence and ataxia. Rosman *et al*. (1993) documented that 25–30% of the children on intermittent oral diazepam developed ataxia, lethargy and irritability, and 5% had speech abnormalities, sleep disorders and altered activity. Furthermore, diazepam given at the time of febrile illness might mask an underlying infection by causing lethargy that is wrongly attributed to the drug (Baumann & Duffner 2000).

CONCLUSIONS

- Febrile convulsions occur in about 2–5% of children.
- The risk of recurrence of febrile convulsions is on average about 30%, but varies depending on the number of risk factors in any given patient.
- There is no risk of brain damage secondary to febrile seizures unless the patient develops febrile status epilepticus.
- The risk of developing epilepsy is about 6%, but this depends on the presence and number of risk factors in any given patient.
- The immediate treatment of febrile convulsions (when the seizure does not spontaneously stop quickly) is intravenous, and if not possible rectal, diazepam. Febrile status epilepticus requires the use of additional medications such as intravenous phenobarbitone.
- Long-term antiepileptic drug therapy is not recommended for the prevention of further febrile convulsions, or the development of epilepsy, because it is either ineffective or has unacceptable adverse effects.
- Exceptions to the above treatment recommendations may include, on an individual basis, intermittent oral diazepam at the time of febrile illnesses in children with high parental anxiety, and continuous phenobarbitone or valproate prophylaxis in children with complex febrile seizures and multiple risk factors that increase their chance of later epilepsy..

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