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CLINICAL REVIEW

Febrile seizures

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The International League Against Epilepsy (ILAE) defines a febrile seizure as "a seizure occurring in childhood after one month of age associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures."[1] The cumulative incidence of febrile seizures is estimated between 2% and 5% in the US and Western Europe,[2 3] between 6% to 9% in Japan, and 14% in India and Guam.[1] Febrile seizures have a peak incidence at 18 months and are most common between the ages of 6 months and 6 years.[4-6]

This review aims to summarise how to recognise a febrile seizure and rule out other underlying causes, how to manage febrile seizures and how to deal with common questions posed by parents in this situation.

Was it a febrile seizure?

Take the child's temperature after the seizure has ended. Beware an alternative diagnosis if the fever is less than 38.0°C.[7] The fever can occur at any time and sometimes after the seizure. Children with febrile seizures have higher temperatures with illness compared with febrile controls.[6] Seizure types include tonic or clonic movement which may be asymmetrical or brief suspensions of awareness. Other events may mimic febrile seizures, and careful history-taking helps distinguish these: fever may be associated with rigors or delirium; a period of pallor and low tone before tonic or clonic movement is suggestive of syncope or a reflex anoxic seizure. Clusters of afebrile seizures in the setting of gastroenteritis, particularly rotavirus infection, are a separate but well recognised entity.

Seizure classification

In 2010 the ILAE proposed that febrile seizures could be organised by typical age at onset (that is, infancy and childhood. Conventionally febrile seizures have been classified as simple or complex based on duration, recurrence, and the presence of focal features (see table⇓). Most febrile seizures are generalised tonic-clonic seizures, and about 30-35% of febrile seizures have one or more complex features (focal onset, duration >10 minutes, or multiple seizures during the illness episode).[6] Febrile status epilepticus, a subgroup of complex febrile seizures with seizures lasting more than 30 minutes, occur in about 5% of cases.[6]

What causes febrile seizure?

Causation is thought to be multifactorial with environmental factors and increasing evidence for genetic factors contributing to pathogenesis.[8 9] The background prevalence risk of 1 in 30 rises to 1 in 5 where one sibling is affected and 1 in 3 if both parents and a previous child have had febrile seizures.[10]

It was previously thought that the rapid onset of high temperature was responsible for provoking febrile seizures, but this is no longer the case.[11] Prophylactic antipyretics do not reduce recurrence risk.[12] Fever may increase brain temperature as a result of the release of inflammatory mediators such as cytokines,[13 14] but it is not clear how the inflammatory mediators induce seizures. Clinical studies, which compared the concentration of cytokines (interleukins 1β and 6) and tumour necrosis factor α in brain or blood in children with and without seizures, showed contradictory results.[15-17]

No single susceptibility gene for febrile seizures is known. In contrast, gene identification has been successful in families with genetic epilepsies with febrile seizures plus (GEFS+). GEFS+ is a familial epilepsy syndrome with a wide range of fever related epilepsies described, notably febrile seizures plus (FS+),[18-20] in which febrile seizures persist beyond the age of 6 years. Here mutations have been found in *SCN1A* and *SCN1B* (both sodium channel genes important for neurotransmission) and *GABRG2* (related to γ-aminobutyric acid, an important inhibitory neurotransmitter).[9 21-27] Dravet syndrome (severe myoclonic epilepsy of infancy), a neurodevelopmental disorder

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The bottom line

- Febrile seizures are the commonest childhood seizure
- There is a low risk (1 in 40) of developing epilepsy in simple febrile seizures
- Benzodiazepines can be used as rescue treatment for recurrent prolonged febrile seizures
- There is no evidence of benefit for prophylactic antiepileptic drugs
- Children with simple febrile seizures have good cognitive outcomes
- Some children with recurrent or prolonged febrile seizures may have some memory impairment. It is not yet clear if this is permanent or if they "catch up" in time

Sources and selection criteria

To prepare this review, we consulted the Cochrane Collaboration and Medline and Embase search engines for articles from 2004 onwards. Key words of "febrile convulsion" and "febrile seizure" were used. We also searched these databases before 2004 using similar medical search headings. We focused on high quality randomised controlled trials, meta-analyses, and systematic reviews.

with intractable seizures,[28] often begins with prolonged seizures triggered by fever.[18 27] The seizure pattern changes with age as myoclonic and later focal seizures evolve. Developmental impairment becomes apparent with time. Dravet syndrome is therefore a form of GEFS+, where mutations in *SCN1A* arise de novo.

How can I be sure this is really a febrile seizure?

A major concern in any febrile child with a seizure is the possibility of central nervous system infection. A seizure in a febrile child can be the only presentation of bacterial meningitis.[29 30] Since the introduction of vaccines for *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, the incidence of bacterial meningitis is substantially reduced. According to a recent systematic review, the overall risk of bacterial meningitis was 0.2% in children with an apparent first simple febrile seizure and 0.6% in children with complex febrile seizure.[31]

As the incidence of bacterial meningitis is low in children with febrile seizures, a lumbar puncture is not indicated routinely. The diagnosis of bacterial meningitis should be based on detailed history taking, thorough clinical examination and the exercise of clinical judgement (see box 1).

What other investigations should be considered?

When central nervous system infection is excluded, the clinician should consider other causes of fever. Although it has been shown that febrile seizures are more likely to occur with respiratory illnesses,[34] any febrile illness may be the cause. Viral upper respiratory infection, otitis media, pneumonia, and gastroenteritis are all common. Urine analysis and urine culture should be considered if a source of infection is not otherwise identifiable.[33] Blood tests (urea and electrolytes profile, full blood count) do not need to be performed routinely. The National Institute for Health and Care Excellence (NICE) offers guidance on the investigation of the febrile child.[7]

Is there a link between febrile seizures and epilepsy?

Febrile seizures can be the first presentation of epilepsy. Careful history and examination will help identify children with an underlying neurological condition. Suspicion of epilepsy should be raised if there was no compelling history of fever, if the seizure was complex or there were postictal signs, or if the child's development is not age appropriate. Although electroencephalography is not routinely indicated, neuroimaging should be considered in those with prolonged postictal neurological deficits or recurrent complex febrile seizures, and in children with developmental impairment or with signs of a neurocutaneous syndrome.[35]

What is the risk of recurrence of febrile seizures?

Parents should be told that febrile seizures may reoccur. Several cohort studies have found that up to a third of children have a recurrence, and 75% of these occur within one year.[8 36] Risk factors for and risk of recurrence after an initial febrile seizure are provided in box 2. Children with all of these risk factors have up to an 80% chance of having further episodes. Children with none of the cited risk factors have a 4% chance of having a further febrile seizure.[8 36-38]

Increased recurrence risk is associated with young age at onset (<18 months), history of a febrile seizures with a temperature at onset of <39°C, and attendance at a day nursery (presumably reflecting increased viral exposure).[41 42] Of these, age at onset seems the most constant predictive factor, with 50% of children aged <12 months and 30% of children aged >12 months presenting with a recurrent febrile seizure. A positive family history of epilepsy is not consistently associated with increased recurrence of simple febrile seizure.[41]

What is the risk of developing epilepsy?

Most children with febrile seizures do not develop epilepsy. An epidemiological study of a cohort of 687 children with an initial febrile seizure (simple and complex) showed a fivefold increased risk of developing unprovoked seizures compared with children with no febrile seizures.[43] The risk ranged from 2.4% among children with simple febrile seizures to 6-8% among children with febrile seizures with a single complex feature.

The risk factors for developing epilepsy are distinct from those that are linked to the recurrence of febrile seizures. The three main risk factors are family history of epilepsy, complex febrile seizures, and neurodevelopmental impairment. Studies have shown that having all three of these risks may increase the risk of developing epilepsy to almost 50%.[3 43-45] A retrospective study of 204 children with febrile seizures in the South Korean population identified the same risk factors: late onset of febrile seizures (age >3 years) and febrile seizures with a temperature of <39°C were also significant predictors of unprovoked

Box 1: Red flags suggestive of central nervous system infection[31-33]

- History of irritability, decreased feeding, or lethargy
- Complex febrile seizures
- Any physical signs of meningitis or encephalitis (bulging fontanelle, neck stiffness, photophobia, focal neurological signs)
- Prolonged postictal altered consciousness or neurological deficit (>1 hour)
- Drowsiness with limited response to social cues (lasting >1 hour)
- Previous or current treatment with antibiotics
- Incomplete immunisation in children aged 6-18 months against *Haemophilus influenzae* b and *Streptococcus pneumoniae*
- In children <2 years old, symptoms and signs of meningeal irritation such as meningism and photophobia may be absent in meningitis and further assessment by a senior paediatrician (or general practitioner with suitable training, depending on the setting) may be required. If there is genuine uncertainty, a lumbar puncture should be performed but postponed if there is reduced consciousness

Box 2: Risk factors for recurrent febrile seizures[10 36-40]

- Age at onset under 18 months
- History of febrile seizure in a first degree relative
- Relatively low grade of fever associated with seizure (<39°C)
- Shorter duration of fever before seizure (<1 hour)
- Multiple seizures during the same febrile illness
- Day nursery attendance

seizures.[46] Knowledge of these risk factors aid the counselling of parents, who often ask if their child is going to develop epilepsy.

Despite retrospective analyses demonstrating that as many as 35% of adults with temporal lobe epilepsy have a history of complex or prolonged febrile seizures in childhood,[47 48] deducing a causal link remains difficult and controversial. One theory suggests that prolonged febrile seizures cause hippocampal volume loss,[49-51] seen on subsequent magnetic resonance imaging. Another hypothesis is that the seizure is due to a pre-existing, previously undetected hippocampal abnormality, caused by an earlier insult or genetic predisposition.[52 53]. Data from prospective outcome studies of febrile status epilepticus in children have been inconclusive and show contradictory results.[43 53-56] Further research is required.

When should we use benzodiazepines?

After a first prolonged febrile seizure, or in a child with other factors giving a high risk of recurrence, benzodiazepines (buccal midazolam or rectal diazepam) should be provided to parents on discharge. These should be used in case of an emergency at home, and parents should be given clear advice regarding when and how to use these rescue medications. The usual recommendation is that rescue medication is given if a seizure is continuing beyond 5 minutes from onset.[43 56]

Most febrile seizures last less than 10 minutes. Even recurrent brief febrile seizures do not warrant treatment as there is no increased risk of brain injury. Febrile status epilepticus (seizure >30 minutes) encompasses 5% of febrile seizures[6] and represents a quarter of all paediatric status epilepticus.[40] It is a risk factor for further prolonged seizures. There may be associated hypoxia, and early termination is important.

The prospective FEBSTAT study included 179 children, aged from 1 month to 6 years presenting with a febrile seizure lasting 30 minutes or more. The study demonstrated that the longer a seizure continues, the less likely it is to stop spontaneously.[57 58] Febrile status epilepticus is not often treated in the time before hospital admission, reflecting concern that benzodiazepines can cause respiratory depression. FEBSTAT showed the need for respiratory support was actually more common in children with longer seizures. Other studies showed that benzodiazepine treatment of seizure either before hospital arrival or in the emergency department setting did not increase the need for intubation.[59 60]

Management of febrile seizures and what to tell parents

Febrile seizures are usually a very frightening experience for parents but it is crucial to highlight that they are not dangerous and their child will not die from the condition.[61-63] They need advice on the common nature of febrile seizures, the rare association with epilepsy, and reassurance that the tendency diminishes with age as the brain matures. Given the 1 in 3 risk of recurrence, it is important to advise parents on what to do if further febrile seizures occur at home (box 3). Information leaflets (see resources) aid recall.

Is there a role for prophylactic drug management?

Antipyretics and antiepileptic drugs have been used to prevent recurrence. These interventions were the subject of a Cochrane review in 2012.[65] Randomised trials were reviewed and outcomes assessed as seizure recurrence rates at ages of 6, 12, 18, 24, and 36 months and at 5-6 years in intervention and non-intervention groups. Intervention groups included children who received antipyretics or antiepileptic drugs either intermittently (only at times of fever recurrence) or, in the case of antiepileptics, as continuous prophylaxis. Adverse medication effects were assessed in order to compare treatment risks versus benefits.

The systematic review demonstrated no advantage in the use of intermittent ibuprofen, diclofenac, or paracetamol versus placebo in preventing further febrile seizures,[65] a conclusion also drawn by a more recent systematic review.[12] This may be particularly useful as advice for worried parents, who may blame themselves for not administering antipyretics before their child had a febrile seizure.

Given the usually benign nature of febrile seizures and the high risk of adverse effects with medications, there currently is no role for prophylactic antiepileptic drugs in preventing recurrent febrile seizures. No benefit has been shown for the use of

Box 3: Advice for parents on initial management of febrile seizures at home[64]

- Protect the child from injury during the seizure
- Do not restrain the child or put anything in the mouth
- Check the airway and place the child in the recovery position when the seizure stops
- Explain that the child may be sleepy for up to an hour after the seizure
- Seek medical advice if a seizure lasts less than 5 minutes or call an ambulance if the seizure continues for more than 5 minutes
- For a recurrent febrile seizure, administer rescue treatment if the tonic-clonic component last longer than 5 minutes
- Administer buccal midazolam as first line treatment or rectal diazepam if preferred or midazolam is not available
- Parents of children with a high risk of recurrence should receive appropriate training

intermittent oral and rectal diazepam, phenytoin, phenobarbitone, sodium valproate, pyridoxine, and intermittent phenobarbitone versus placebo in preventing febrile seizures. Intermittent clobazam versus placebo at 6 months showed an apparent benefit, but in the control group the recurrence rate of febrile seizures was extremely high at 83.3%, and this result therefore needs replication.[65] More importantly, adverse medication effects were found in up to 30% of recipients.

What is the role of antipyretics?

Tepid sponging is no longer recommended for febrile children as it may raise core body temperature. Children should not be underdressed nor overdressed.[7] Antipyretics should be used to relieve the distress of feeling ill.[7] Prophylactic use does not reduce recurrence risk.

Do febrile seizures have an effect on cognition?

Parents should be reassured that having a single simple febrile seizure does not pose a threat to a child's cognitive development. Previous population studies have demonstrated normal cognition and intellect in this group of children.[50 66] A UK population based study, which included 381 children with febrile seizures (287 with simple and 94 with complex febrile seizures) reported that those with febrile seizures perform as well as other children in academic performance, intellectually (British ability scales), and behaviourally when assessed at 10 years of age.[66]

A 2012 population based cohort study in Rotterdam showed that febrile seizures were not associated with an increased risk of behavioural difficulties or problems in executive functioning.[62] However, children with recurrent febrile seizures, in contrast to those who had a single seizure, had an increased risk of delayed language development. A study of 26 children with prolonged febrile seizures, 15 of whom were followed for an average of one year after their seizure, showed an increased risk of recognition memory impairment. This suggests that memory impairments are not a transient effect of prolonged febrile seizures.[63]

These studies show that the outcome of simple febrile seizures is generally benign, but in children with recurrent or prolonged febrile seizures this may not be the case. Parents should be cautioned about this so that appropriate developmental support is in place should it be required.

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When to seek specialist opinion

Most children with febrile seizures do not require hospital admission. The incidence of bacterial meningitis is low, and clinical features can help distinguish between the two.

We recommend that children with febrile seizures should have further assessment by a paediatrician (or general practitioner with suitable training, depending on the setting) if they develop

- First febrile seizure
- Decreased consciousness level before seizure (use of the Paediatric Glasgow Coma Score is encouraged for an objective record)
- Slow recovery with abnormal behaviour or drowsiness after seizure (consider referral if normal neurological or mental state is not achieved within one hour)
- Clinical signs of meningism (irritability, neck stiffness, photophobia, headache)
- Complex febrile seizures
- Focal neurological deficit on examination
- Unwell child with features of septicaemia
- Unexplained cause of fever

Additional educational resources

Information resources for clinicians

- Patient UK. Febrile convulsions. www.patient.co.uk/doctor/febrile-convulsions
  Collated information on febrile seizure
- Medscape. Pediatric febrile seizures. http://emedicine.medscape.com/article/1176205-overview
  Collated information on febrile seizure
- NICE Clinical Knowledge Summaries. Febrile seizure. Scenario: Management after a seizure. http://cks.nice.org.uk/febrile-seizure#!scenariorecommendation
  A NICE Clinical Knowledge Summary
- Royal Children's Hospital Melbourne. Febrile convulsion. www.rch.org.au/clinicalguide/guideline_index/Febrile_Convulsion/
  Summary of acute clinical management
- Nottingham Children's Hospital. Febrile seizure guideline. https://www.nuh.nhs.uk/handlers/downloads.ashx?id=43969
  Clinical guideline with treatment algorithm

Information resources for patients

- NHS choices. Febrile seizures. www.nhs.uk/conditions/Febrile-convulsions/Pages/Introduction.aspx
  Comprehensive, well laid out summary of febrile seizure presentation and management
- Guy's and St Thomas' NHS Foundation Trust. Febrile convulsions: Information for parents and carers. www.evelinalondon.nhs.uk/resources/patient-information/febrile-convulsion.pdf
  Parents' common questions answered
- Patient UK: Febrile seizure (febrile convulsion). www.patient.co.uk/health/febrile-seizure-febrile-convulsion
  Useful advice for parents
- AboutKidsHealth. Febrile seizures (convulsions caused by fever). www.aboutkidshealth.ca/en/healthaz/conditionsanddiseases/brainandnervoussystemdisorders/pages/febrile-seizures-convulsions-caused-by-fever.aspx
  Short summary, primarily of what to do in the case of acute seizure
- Royal Children's Hospital Melbourne: Febrile convulsions. www.rch.org.au/kidsinfo/fact_sheets/Febrile_Convulsions/
  A bulleted fact sheet on care of acute seizure

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Table

Table 1| Key features differentiating simple febrile seizures from complex febrile seizures

Feature	Simple febrile seizures	Complex febrile seizures
Duration	Short (<15 minutes)	Longer (>15 minutes)
Focal features	Generalised tonic-clonic features are typical (stiffening of muscles followed by rhythmical jerking or shaking)	Focal seizures with or without secondary generalisation
Recurrence	No recurrence within the next 24 hours	May present with repetitive seizures during the next 24 hours
Postictal features	No postictal pathology	Todd's paresis may be present (a period of paresis of affected limbs)