MorningReport

Febrile Seizures

MorningReport

Brad Sobolewski, MD, MEd

Professor

Division of Emergency Medicine

What are febrile seizures and how common are they?

Febrile seizures

You see them every shift

- The most common neurologic disorder of infants and young children
- Convulsion associated with a temperature greater than 38°C
- Occur in 2-4% of children between 6 months and 5 years of age
- Peak incidence 12 to 18 months with Male:Female ratio 1.6:1
- No history of previous afebrile seizures
- No CNS infection or inflammation, or systemic metabolic abnormality (hypoglycemia, hyponatremia)

Why do they happen?

We don’t know…

All across the myelin nation

- Likely related to a vulnerability of the developing nervous system to the effects of fever
- The neurons that generate these seizures aren’t completely myelinated until age 6
- Neurons are more hyperexcitable (by cytokines during fever) in younger children who get sick more often
- Underlying genetic susceptibility plays a role

Risk factors

I didn’t know he had a fever!

- High fever
- Viral infection
- Recent immunization
- Family history of febrile seizures
- Prenatal exposure to nicotine
- Atopic diseases
- *Maybe* iron deficiency anemia

Seizures are often seen as the temperature is increasing rapidly, but the **degree of fever**, **not the rate of temperature rise**, is the precipitating stimulus

-Millichap, *Pediatrics*, 1959

Timing of febrile seizures? Height of fever?

Never at the opportune moment

- Majority of children have febrile seizures on the first day of illness
- In some cases it is the first manifestation of illness
- Degree of fever associated with febrile seizures is variable and depends on the child's threshold convulsive temperature
- Fever is most often ≥39ºC - but 25% occur between 38-39ºC
- In a study of 110 children temp with febrile seizures was significantly higher than the mean temp of febrile illness with no seizures (104.0 vs 103.3°F, $p<0.001$)
- Seizure threshold is lower in infants who have more febrile illnesses

Viral infection

It’s just a virus

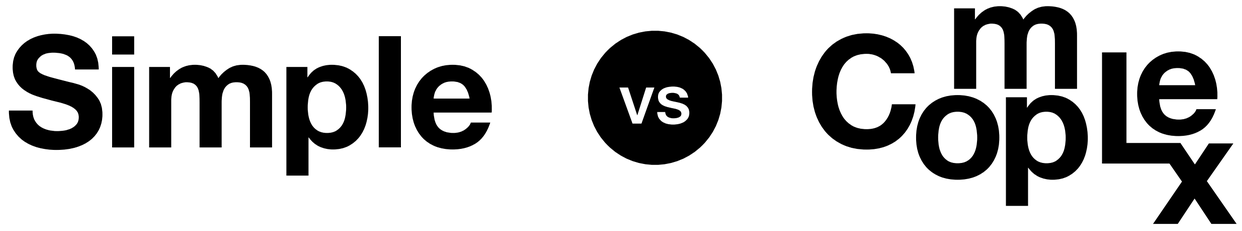
- HHV-6 is the cause in ⅓ of all first-time febrile seizures in US children <2 years of age
  - The mean maximum fever in infants with primary HHV-6 infection is generally ≥39.5°C (103°F)
  - Incidence of febrile seizures in primary HHV-6 infection is ~36% in 12-15 month olds
- Other common causes: adenovirus, RSV, HSV, CMV, HHV-7 - in Asia Influenza A is #1
- The type of viral infection is not important in predicting future recurrence of a febrile seizure or a complex febrile seizure
- Breastfeeding is reported as a protective factor up to age 2.5 years

Recent immunizations?

Vaccines don’t case autism, but febrile seizures?

- The risk of febrile seizures is increased after administration diphtheria, tetanus toxoid, and whole-cell pertussis (DTwP), and measles, mumps, and rubella (MMR), and MMR with varicella
- The absolute risk is small
- Genetic susceptibility may also play a role in seizures after vaccines
- The risk of a future febrile seizure with a subsequent vaccine is lower than the risks of the disease you are vaccinating against
- In drug company sponsored studies the absolute risk of a febrile seizure after MMRV is 3-4 seizures for every 100,000 children receiving the vaccine

How do we categorize them?


Simple
vs
Complex

Simple

Complex

Generalized

Focal?

Yes
Shaking limited to one limb
or one side of the body

<15 minutes
<10 minutes has been proposed

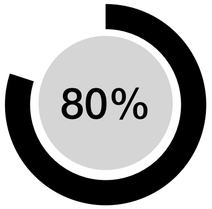
Duration

>15 minutes

Single episode

Recurrence within 24 hours

More than once



History may or may not be reliable

Can I get a witness?

- Seizure characteristics
- Duration of the seizure
- Did they record it?
- Any underlying medical conditions, neurologic or developmental problems
- Immunization status

Is it that straightforward?

Not so simple…

- The term **simple** undersells how scary this is for families
- Why does the **complex** category contain so much heterogeneity?
  - Two one-minute seizures an hour apart in a well appearing child?
  - Focal one-sided convulsions?
  - Febrile status epilepticus?

What is the recurrence risk?

Febrile seizure recurrence risk

It’s all coming back to me…

- Overall recurrence rate is approximately 30-35%
- If you have 2 or more you have a 50% chance of subsequent febrile seizures
- The subsequent seizure is almost always similar to the first - 95% of initial simple have recurrent simple febrile seizures
- As high as 50-65% in children ≤12 months at time of first seizure
- <20% in older children

Febrile seizure recurrence risk

Back to where it all started…

- Factors for increased recurrence risk
    - Young age at onset
    - History of febrile seizures in a first-degree relative
    - Low degree of fever while in the emergency department
    - Brief duration between the onset of fever and the initial seizure

What is the risk of epilepsy following febrile seizures?

If you have one simple febrile seizure your risk of epilepsy is…

# of humans have epilepsy

Risk of epilepsy after febrile seizures

Rates may vary

- In a normal child with a simple febrile seizure, the risk is ~1-2%
- Abnormal developmental history, or a family history of epilepsy - risk is ~5-10%
- If first seizure is complex the risk of epilepsy is 18x simple febrile seizures
- Risk of developing epilepsy is greatest in first 5 years following febrile seizure

What is the evaluation and management for simple febrile seizures?

Discharge home?

Simple febrile seizures don’t require Neurology consults or admission

Do not order laboratory testing or a CT scan of the head for a patient with an unprovoked, generalized seizure or a simple febrile seizure who has returned to baseline mental status

Choosing Wisely®

Labs are not necessary in simple febrile seizures

You can “Choose Wisely”

- Post-ictal period is usually brief ~20-30 minutes to 2 hours
- Patients should return to neurologic baseline with a normal Neuro exam
- Labs are painful, expensive, & can give us erroneous, unexpected, and irrelevant results

Labs?

The cost adds up!

Rapid glucose $60

- If the patient is transported by EMS following a seizure it is highly likely they have one.

Blood gas ≥$300

- In the immediate post-seizure period you're likely to see respiratory acidosis - but if they are now breathing on their own what are you going to do about it? Send another one to provide its normal?

Renal panel (chem 7) ≥$120

- A representative retrospective single centre cross-sectional study, involving 549 children with simple febrile seizures, evaluated potential laboratory abnormalities. The study showed that 99.3% of blood glucose level, 98% of calcium, and 99% of electrolytes and renal function tests were normal

Labs?

The cost adds up!

CBC with differential ~$60

- You could see an acute stress response with elevated WBC after a seizures *and* it doesn't tell you what kind of infection the child has

Viral testing $150-400+

- Useful if you are concerned about specific entities such as flu or covid & clinical diagnosis is uncertain
- Big comprehensive panels are >$1300-1600USD (more on that in a bit)

Urinalysis ~$60 / Urine Culture ~$90-100

- Follow UTI testing guidelines and use **UTICalc.com** in your fever workup
- My hospital defaults to urinalysis with reflex to culture only if positive urinalysis

Lumbar puncture $500-1000

Imaging?

The data is lower quality than the images themselves

- In general there are **low quality observational studies** looking at the general use of CT for children
- Overall the risk of **scarring**, **inflammatory/infective/immune abnormalities, and tumors** are all **<1%**
- In the absence of concerning signs on history and examination the rate of the abnormalities is very low
- **Head CT up to $1800** & **MRI $1800 to ≥$3600**

What is the evaluation and management for complex febrile seizures?

Every patient who has a complex febrile seizure needs an individualized treatment and disposition plan, generally developed with the guidance of Pediatric Neurology

Complex management

Again: focal onset, prolonged, or recurrent within 24 hours

- Majority of children who develop complex febrile seizures do so with their first seizure
- Transient hemiparesis following a febrile seizure (Todd's paresis), usually of complex or focal type, is rare, 0.4-2% of cases
- Prolonged or focal febrile seizures have a higher likelihood of meningitis or structural abnormality - but the risk is still quite low
- EEG and MRI following the ED visit may be the only tests these children need

Lumbar puncture

The AAP subcommittee on febrile seizures is a thing

- LP/CSF studies to exclude meningitis or encephalitis in febrile seizure is based mainly on clinical signs
- ~25% of children with meningitis will have seizures at or before the initial presentation
- Almost all of them will have other signs and symptoms of meningitis (eg, altered consciousness, nuchal rigidity, petechial rash)
- Febrile seizures after the the second day of illness? Febrile status epilepticus?
- Overall yield of LP is very low - Pleocytosis *can* occur in epileptic seizures, but it is rare in febrile seizures

Admission? Neuro consult?

It depends…

- Previously healthy and developmentally & neurologically normal children with two brief self-resolved seizures can be discharged home
  - PRN Neuro referral is OK if you and family are comfortable
- Febrile status epilepticus - always admit to Neuro/PICU
- Complex febrile seizures with focal features - strongly consider admission and always discuss with Neuro

Neurology referral

P NEU REFERRAL

- Neurology will see children in the near term with complex febrile seizures who you feel are safe for discharge but need evaluation
- Abnormalities are more likely to be seen on EEG when the test is performed shortly after the seizure (<10 days) and when convulsions are of long duration and have focal features
- EEG is not useful in determining the risk of recurrent febrile seizures

“Any female patient under 12 months of age with complex febrile seizures has Dravet Syndrome until proven otherwise.”

Kris Wesselkamper, MD - Pediatric Neurologist, Cincinnati Children’s

Dravet syndrome

AKA - Severe myoclonic epilepsy of infancy

- Can resemble complex febrile seizures in the first year
- De-novo mutations in a voltage-gated sodium channel in 80% of patients
- This is why fosphenytoin doesn’t work in Dravet syndrome
- First year of life - prolonged, often febrile, generalized clonic or hemiclonic seizures
- Normal cognitive and motor development prior to the onset of seizures
- First seizure is afebrile at least one-third of the time
- Leads to refractory seizures and poor neurodevelopmental outcomes

What about febrile status epilepticus?

Status epilepticus management for 29 days or older

Status Epilepticus defined as persistent seizure activity or intermittent activity without return to baseline between episodes that last for more than 5 minutes

Establish ABCs (maintain airway, provide oxygen, support ventilation as needed)
Attach patient to monitor, pulse oximetry and ETCO2 monitor
Obtain IV/IO access; Obtain FSBS, I-stat and red top tube (to be sent for AED levels if applicable)
Correct Hypoglycemia, Hyponatremia and/or Hypocalcemia, as indicated

First Line Therapy*

If have IV/IO access, give Lorazepam (Ativan) 0.1mg/kg IV push over 2 min (max 4mg)[2]

If no IV/IO access, give Midazolam (Versed) IM[1] as follows: 10mg for >40kg, 5mg for 13-40kg, or 0.2mg/kg for <13kg

Seizure abates → **Continue close observation**

Ensure adequate oxygenation and ventilation

Manage airway as clinically indicated

Consider I-stat to re-measure PCO2

Discuss further management with Neurology

Still seizing after 5 min

Second Line Therapy

If have IV/IO access, give Lorazepam (Ativan) 0.1mg/kg IV push over 2 min (max 4mg)[2]

If no IV/IO access, give Midazolam (Versed) IM[1] as follows: 10mg for >40kg, 5mg for 13-40kg, or 0.2mg/kg for <13kg

Seizure abates

Consult Neurology (page fellow)

Still seizing after 5 min

Levetiracetam (Keppra) 60mg/kg IV (max 4500mg) via infusion over 5 minutes

Other options for 2nd line therapy, based on discussions with Neurology or parents:

- Fosphenytoin 20mg PE/kg IV (max 1500mg PE) via infusion over 10 minutes
- Valproate (Depacon) 40mg/kg IV (max 3000mg) via infusion over 10 minutes

Seizure abates

Still seizing 10 min after infusion is complete

Third Line Therapy

Start **Midazolam 0.2mg/kg IV bolus** (Max 10mg), then **0.2mg/kg/hour (Max 10mg/hour) IV infusion** (drip available in STS Pyxis or order in EPIC to come from Pharmacy). Increase infusion rate by 0.2mg/kg/hour (Max 10mg/ hour) every 10 min until burst suppression or reach a maximum dose of 2mg/kg/hour (Max 100 mg/hour)

Seizure abates

Consult PICU & arrange for continuous EEG

Perform endotracheal intubation if not already done

Other considerations

[1]Can give Midazolam IN (IM is preferred)

*If do not have access to Lorazepam or Midazolam, can then choose one of these as first line therapy:

- IV Phenobarbital 15mg/kg/dose x 1
- PR Diazepam 0.2-0.5 mg/kg (max20 mg/dose)

[2]If already received dose(s) of benzodiazepine at home or via EMS; then only give one dose in ED before proceeding to 2nd line therapy box

Consider IV glucose (avoid in patient on ketogenic diet), naloxone or pyridoxine based on clinical scenario if seizure refractory to therapy

Strongly consider EEG if concern for subclinical status – must be arranged by neurology fellow

[3]Home AED therapy will not change acute management of status epilepticus except for known contraindication for recommended therapies (e.g., allergy, no fosphenytoin for Dravet's, no IV glucose for ketogenic diet)

This is a guideline only and has been developed by the Medical Resuscitation Committee of the Division of Emergency Medicine and the Status Epilepticus Committee of CCHMC. *Last updated Feb 2023* - **see page 2 for more details**.

Cincinnati Children's
changing the outcome together

MEDICAL RESUSCITATION COMMITTEE
STS
SHOCK TRAUMA SUITE ALGORITHMS

Are febrile seizures associated with an increased risk of mortality?

Mortality risk

Relevant to the parents' fears

- Early reports suggested febrile seizures were associated with an increased risk of sudden death
- Small excess in mortality is restricted to complex febrile seizures - but really in patients with preexisting neurologic abnormalities and subsequent epilepsy
- Overall the association of **febrile seizures** with the risk of sudden death remains uncertain but very low

Is there a role for preventative therapy / rescue drugs?

Rescue drugs?

Benzo in the end zone

- Children with a history of prolonged febrile seizure, including febrile status epilepticus, diazepam rectal gel (0.5 mg/kg) can be prescribed and administered for seizures ≥5minutes
- One dose administered rectally will not lead to respiratory depression
- Midazolam nasal spray is an alternative to rectal diazepam for home use
- In general children with risk of prolonged future febrile seizures or baseline neurologic ardor developmental problems are good candidates for rescue meds

.CWSZInstructions

Epic smart phrase from Child Neurologist Cameron Wade with patient and family information and materials on rescue drug instructions and options

Prophylactic AEDs can decrease the risk of recurrent febrile seizures

but

Most febrile seizures are benign

and

Side effects of AEDs generally outweigh the benefits

Preventative therapy / antipyretics

Chill out…

- Use of antipyretics at the first sign of fever does not prevent recurrent febrile seizures
- A single center prospective RCT from Murata et al, *Pediatrics*, 2018 noted that regular antipyretics may reduce the recurrence of febrile seizures during the same fever episode
    - Randomly assigned to acetaminophen (10 mg/kg by suppository every six hours until 24 hours after febrile seizure onset if temperature remained >38.0° C) or to no antipyretic treatment
- Rosenbloom et al in *Eur J Paediatr Neurol*, 2013
    - Meta-analysis of 3 RCTs & 540 patients concluded that antipyretics (acetaminophen, ibuprofen, or diclofenac) were ineffective in reducing the rate of recurrent febrile seizures, compared with placebo
    - Risk of recurrent febrile seizure was 23% in antipyretics group, 24% in placebo

How do we talk to families about febrile seizures?

How to talk to families

Remember, they are scared!

- Acknowledge that this was perhaps the scariest thing they've ever seen their child do!
- The caregiver may have felt helpless - but reinforce what they did **right**
- Define what a seizure is in ways they'll understand - including how common febrile seizures are
- Explain how the body **protects itself** during seizures
  - Sympathetic surge leading to increased heart rate
  - Pale skin due to peripheral vasoconstriction and shunting blood to the core
  - Closed glottis protects from aspiration, which can lead to perioral cyanosis

How to talk to families

This is our most important job

- Describe febrile seizures and what category their child falls into into a way they can explain
- Discuss the recurrence risk and what to do it it happens again
- Talk about the use of antipyretics and their limited impact on recurrence (only during *this* current illness based on the best current evidence)
- Use lab testing judiciously, not just to “make sure everything’s okay”

Parents and caregivers should be reassured that since their child has returned to normal, further investigations (labs and CT) are unlikely to identify anything that a careful history or examination would not pick up (patients with no red flags won’t have a tumor on CT)

Febrile Seizures

MorningReport