To seize, or not to seize....
Common Neurologic Problems for the Generalist and Update on Seizure Management

DONITA LIGHTNER, MD
ASSISTANT PROFESSOR
CHILD NEUROLOGY AND NEURO-ONCOLOGY
DEPARTMENT OF NEUROLOGY
UNIVERSITY OF KENTUCKY
LEXINGTON, KY

Faculty Disclosure

- I have nothing to disclose.
Educational Need

- Patients will present to their primary care provider for atypical spells before they ever see a **neurologist**
- Primary care providers need to know basic treatments for epilepsy

Objectives

Upon completion of this educational activity, you will know:
- Basic statistics for epilepsy
- How to better triage patients
- More about antiepileptic medications
5y boy with no significant PMH presents to your office with new onset GTC seizure.
- Lasted 1-2 minutes
- No signs of illness
- He has never done this before.
- He is currently back to baseline

- Born at term
- Normal development
- No family history of epilepsy or genetic disease.
  - Mom has migraines.
- Normal exam
- Mom is wigging out!!!

What do you do?
**What is a first unprovoked seizure?**

- The International League Against Epilepsy (ILAE) defines as follows:
  - Seizure or flurry of seizures all occurring within 24 hours
  - Person over 1 month of age
  - No prior history of unprovoked seizures

**What is epilepsy?**

- Recurrent, unprovoked seizures
- Generalized
- Partial
Statistics

- Epilepsy affects 0.5-1% of children (0-16 years)
- 300,000 patients yearly seek medical attention for new onset seizure in the US
- 120,000 (40%) of these patients are under 18 years of age

*J Child Neurol. 2002 17:S4*

Prognosis

- Prognosis depends upon age of the child
  - First partial motor seizure before age 2y is associated with a recurrence rate of 90%.
  - 25% of children with recurrent seizures in the first year of life are neurologically abnormal at the time of the first seizure.
  - For older children, risk of recurrent seizures or epilepsy ranges from 27 to 52%.

*J Child Neurol. 2002 17:S4*
Recurrence

- 50-80% of recurrent seizures are seen in 6 months to 2 years from the initial ictal event
- Up to 10 years has been seen, but very rare
- If a second seizure happens, then risk thereafter increases to 70%.

*J Child Neurol. 2002 17:S4*

- TIME FOR MEDICATIONS!!!

Case 1

- Rectal diazepam is your friend.
- If a seizure lasts 5 minutes, a family member can administer it.
- Comes in a twin pack.
- Always give refills.
Case 1

- If seizure continues after 10 minutes from administration time, then it can be re-administered.
- 911

Case 2

- 6y girl presents with new onset GTC seizure.
- She is now back to baseline.
- No signs of illness.
- No prior history of GTC seizure.
- ROS: History of ADHD which did not respond to stimulants. She is in special education.
## Case 2
- Born at 35 weeks gestation
- Was involved with First Steps due to toe-walking and has AFO’s in place.
- Now receives therapies through the school system.
- What do you do?

## Risk Factors for Epilepsy
- Cerebral palsy
- Mental retardation or developmental disability
- Autism
- History of CNS infection or traumatic brain injury

*J Child Neurol. 2002 17:S4*
Case 2

- Rectal diazepam is still your friend.
- Levetiracetam is a beautiful medication.
- Liquid or tablet.
- NO METABOLISM
- Biggest side effects are moodiness, irritability, and hyperactivity
- Start low and go slow to 10mg/kg bid.

Common Epilepsy Syndromes

<table>
<thead>
<tr>
<th>Generalized</th>
<th>Partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence</td>
<td>Benign Occipital Epilepsy of Childhood</td>
</tr>
<tr>
<td>Juvenile Absence</td>
<td>Panayiotopoulos Syndrome</td>
</tr>
<tr>
<td>Juvenile Myoclonic Epilepsy</td>
<td>Benign Childhood Epilepsy with Centrottemporal Spikes</td>
</tr>
<tr>
<td>Epilepsy with Generalized Tonic-Clonic Seizures on Awakening</td>
<td>Autosomal Dominant Nocturnal Frontal Lobe Epilepsy</td>
</tr>
<tr>
<td>Jeavons Syndrome</td>
<td>Landau-Kleffner syndrome</td>
</tr>
<tr>
<td></td>
<td>Mesial Temporal Sclerosis</td>
</tr>
</tbody>
</table>

www.epilepsyfoundation.org
Clinical Pediatric Neurology
A Signs and Symptoms Approach
Gerald M. Fenichel
Febrile seizures

9mo girl has a generalized febrile seizure associated with symptoms of an upper respiratory tract infection and a temperature of 102.2.

Of the following, the factor that is MOST likely to increase her chance of epilepsy is having...

- A febrile seizure after 2 years of age
- A rash consistent with roseola
- A seizure that lasts 10 minutes
- Cerebral palsy
- Three febrile seizures in 1 year
PREP Question 2 (2000)

A febrile 15m boy had a 2 minute generalized seizure 1 hour ago. He has had a 1-day history of rhinorrhea and fever up to 104. On exam, he is alert, playful, and drinks from a sippy cup. Mom is concerned about the risk of epilepsy.

Of the following, the factor that is MOST predictive of recurrent febrile seizure is...
- Abnormalities on EEG
- Delay between the onset of fever and the seizure
- Fever greater than 104
- Occurrence of first seizure before 6m of age
- Occurrence of the seizure after DTP vaccine

PREP Question 3 (2001)

You are called to the ED to evaluate a 9m girl who just had a 10-minute GTC. Development has been normal. Physical exam reveals a sleepy, irritable child with temp to 103.1, bilateral OM, and no focal neurological findings.

Of the following, the MOST appropriate diagnostic test to perform is...
- CT of the head
- EEG
- LP
- Measurement of serum calcium
- Urine drug screen
What is a febrile seizure?

- Seizure with fever
- No CNS infection
- No electrolyte abnormalities

Febrile Seizure Statistics

- 2-5% of all children
- 6m to 6y
- Average age 18m-2y
- Half present between 12-30m
Febrile Seizure Statistics

- Of children with febrile seizures:
  - 25-40% have a family history of febrile seizure
  - About 5% have family history of epilepsy

What is a febrile seizure?

<table>
<thead>
<tr>
<th>Simple</th>
<th>Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Less than 15 min</td>
<td>• Longer than 15 minutes</td>
</tr>
<tr>
<td>• Generalized</td>
<td>• Multiple in a 24 hour period</td>
</tr>
<tr>
<td></td>
<td>• Focal features</td>
</tr>
</tbody>
</table>
Simple Febrile Seizures

- No evidence of increased mortality, hemiplegia, or mental retardation
- Risk of epilepsy by age of 7y is only slightly higher than the 1% risk of the general population

Pathophysiology

- Fever appears to lower seizure threshold
- Channelopathy
- Seems to be related to the rate of rise in temperature
- HHV-6 (roseola infantum) and influenza A have been associated with an increased risk of febrile seizures.
Risks of Recurrence

- 30% have recurrent seizure during subsequent illness
  - If there is a second recurrence, about half will have at least one more recurrence
  - Most recurrences happen within one year of the initial seizure

Risks of Recurrence

- Risk factors for recurrence
  - Onset of seizure before 18m
  - Occurrence at lower temperatures
  - Shorter duration of fever before the seizure
  - Family history of febrile seizure
  - If all above are present, ~75% recurrence
Febrile Status Epilepticus: FEBSTAT Study

- Human Herpes 6 and 7 (HHV-6 and HHV-7) account for one third of cases
  

- CSF pleocytosis is not seen
  - 150/200 had nontraumatic LP’s and all findings were normal

  *J Pediatr.* 2012 Dec;161(6):1169-71

Febrile Status Epilepticus: FEBSTAT Study

- EEG in febrile status is important
  - Focal slowing suggests increased risk of hippocampal sclerosis
  - Epileptiform discharges only seen in a small percent

  *Neurology.* 2012 Nov 27;79(22):2180-6
Febrile Status Epilepticus: FEBSTAT Study

- MRI findings
  - 96 children with simple febrile seizures used as controls
  - No changes in signal of hippocampus seen in controls
  - 10% in study group had abnormalities in hippocampus

Neurology. 2012 Aug 28;79(9):871-7

Risks of Development of Epilepsy

- Family history of epilepsy
- History of febrile seizure in parent or sibling
- Complex febrile seizure or febrile status epilepticus
- History of CP, Autism, or developmental delay
Clinical Assessment

- HISTORY! HISTORY! HISTORY!
- Temperatures prior to seizure
- Medications
- Family history
- Neurological exam

Treatment of Simple Febrile Seizures

- Airway, Breathing, Circulation
  - No need for AED’s for children with one or more simple febrile seizures
- Rectal diazepam is your friend.
- Extensive counseling and reassurance for parents
  - Excellent prognosis
  - Simple febrile seizures are benign and common
  - No long term sequelae
  - Antipyretics will not prevent febrile seizures, but will make child more comfortable
AAP Recommendations for Simple Febrile Seizure

- **Lumber puncture**
  - Infants <12m, LP *strongly* considered
  - For 12-18m, LP should be considered (meningeal signs may be subtle)
  - For >18m, LP is recommended only if meningeal signs are present
  - For children who received antibiotic pre-treatment, meningitis could be partially treated and LP should be *strongly* considered.

AAP Recommendations for Simple Febrile Seizure

- EEG should **not** be performed in a neurologically healthy child with one simple febrile seizure
- Lab studies should **not** be routinely performed in a healthy child with first simple febrile seizure.
- Neuroimaging not indicated
PREP Question 1 (1998)

9mo girl has a generalized febrile seizure associated with symptoms of an upper respiratory tract infection and a temperature of 102.2.

Of the following, the factor that is MOST likely to increase her chance of epilepsy is having...
- A febrile seizure after 2 years of age
- A rash consistent with roseola
- A seizure that lasts 10 minutes
- **Cerebral palsy**
- Three febrile seizures in 1 year

PREP Question 2 (2000)

A febrile 15m boy had a 2 minute generalized seizure 1 hour ago. He has had a 1-day history of rhinorrhea and fever up to 104. On exam, he is alert, playful, and drinks from a sippy cup. Mom is concerned about the risk of epilepsy.

Of the following, the factor that is MOST predictive of recurrent febrile seizure is...
- Abnormalities on EEG
- Delay between the onset of fever and the seizure
- Fever greater than 104
- **Occurrence of first seizure before 6m of age**
- Occurrence of the seizure after DTP vaccine
You are called to the ED to evaluate a 9m girl who just had a 10-minute GTC. Development has been normal. Physical exam reveals a sleepy, irritable child with temp to 103.1, bilateral OM, and no focal neurological findings.

Of the following, the MOST appropriate diagnostic test to perform is...
- CT of the head
- EEG
- LP
- Measurement of serum calcium
- Urine drug screen

Complex Febrile Seizures
- Treatment depends on the child and can be debated
- Even if MRI abnormalities are seen, if a child does not have recurrent events, should AED be started?
- If AED’s started early on, can this reverse the natural history of mesial temporal sclerosis (MTS) and epilepsy in adulthood?
- Some mouse models suggest levetiracetam has anti-inflammatory effects.
Seizures in the Setting of Genetic Disease and Tumor Growth Syndromes

Neurofibromatosis

- First described in the eighteenth century
- Von Recklinghausen was the first to use the term neurofibromatosis in 1882
- Incidence is 1 in 3000
- Most common gene defect to affect the nervous system
Neurofibromatosis

- Chromosome 17q11.2
- More than 1000 independent mutations have been reported
  - 60-70% of mutations result in truncated and nonfunctioning protein
  - Somatic mosaicism is common


Neurofibromatosis

- About 5% of all NF1 patients have large deletions of the entire locus and adjacent region
- 3 identified types of recurrent microdeletions:
  - Type 1: 1.4 Mb; 14 genes including NF1
  - Type 2: 1.2 Mb
  - Type 3: 1 Mb
Neurofibromatosis

**Brain malformations**
- Thickening of corpus callosum
- 604 patients studied
  - 5% (31) had brain malformations: Chiari I malformation, hemihypertrophy (2), heterotopia (2), double cortex (1)
  - Children with malformations had IQ<85 (range 52-110)


  - Genetic testing not performed
    - Previous study demonstrated patients with deletion of entire gene and IQ <80. 60% had structural brain abnormalities

Tuberous Sclerosis

- First fully described by Bourneville around 1880
- $TSC_1$ (Hamartin) vs $TSC_2$ (Tuberin)
- About 15% of patients with TS show no identifiable mutation and are milder forms of disease
- Accounts for 0.66% of mentally retarded patients and 0.32% of patients suffering from epilepsy
- Defects in tumor suppressor genes, resulting in numerous lesions
Tuberous Sclerosis

- Cognitive delay may or may not be present
- Cortical tubers
- Subependymal giant cell astrocytomas
- Cutaneous malformations
- Epilepsy
- Autism

Tuberous Sclerosis

- Infantile spasms
- Partial seizures which may or may not secondarily generalize
- May require multiple antiepileptic medications
## Anti-Epileptic Medications

<table>
<thead>
<tr>
<th>Broad Spectrum</th>
<th>Narrow Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Levetiracetam</td>
<td>• Ethosuximide</td>
</tr>
<tr>
<td>• Topiramate</td>
<td>• Oxcarbazepine</td>
</tr>
<tr>
<td>• Zonisamide</td>
<td>• Carbamazepine</td>
</tr>
<tr>
<td>• Lamotrigine</td>
<td>• Phenytoin</td>
</tr>
<tr>
<td>• Valproic acid</td>
<td>• Vigabatrin</td>
</tr>
<tr>
<td>• Rufinamide, Clobazam,</td>
<td>• Tiagabine</td>
</tr>
<tr>
<td>and other benzodiazepines</td>
<td></td>
</tr>
<tr>
<td>• Felbamate</td>
<td></td>
</tr>
<tr>
<td>• Phenobarbital</td>
<td></td>
</tr>
<tr>
<td>• Primidone</td>
<td></td>
</tr>
<tr>
<td>• Lacosamide?</td>
<td></td>
</tr>
</tbody>
</table>
### Common AED’s

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Metabolism</th>
<th>Enzyme Inducer?</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>Blocks sodium channels, enhances GABA(A) activity, antagonizes AMPA/kainate glutamate receptors, weakly inhibits carbonic anhydrase.</td>
<td>Minor liver via hydroxylation</td>
<td>no</td>
<td>Sleepiness, moodiness, irritability, word-finding difficulty, weight loss, nephrolithiasis and acidosis, glaucoma</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Enhances GABA formation; blocks Na, K, Ca channels; inhibits histone deacetylase</td>
<td>Liver</td>
<td>no</td>
<td>Hepatotoxicity, hair loss, thrombocytopenia, pancreatitis, weight gain</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Barbiturate; activates Cl channels to enhance GABA</td>
<td>Liver</td>
<td>yes</td>
<td>Drowsiness, nystagmus, dizziness, behavioral problems</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Enhances slow inactivation of Na channels</td>
<td>Liver</td>
<td>no</td>
<td>Drowsiness, diplopia, nystagmus</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Inhibits T-type Ca channels</td>
<td>Liver</td>
<td>no</td>
<td>Nausea and abdominal pain, rash, moodiness, blood dyscrasias</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Na channel blocker</td>
<td>Liver</td>
<td>yes</td>
<td>Drowsiness, weight gain, diplopia, nystagmus, hyponatremia</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Na channel blocker</td>
<td>Liver with enterohepatic recirculation</td>
<td>yes</td>
<td>Sleepiness, ataxia, diplopia, hypersensitivity, osteoporosis, gingival hyperplasia and coarse facies, peripheral neuropathy</td>
</tr>
</tbody>
</table>
Thank you!

Donita Lightner, MD
Donita.lightner@uky.edu
859-323-5661