PEDIATRIC SEIZURE CASES

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Objectives

- Discuss cases of pediatric seizures that may be common encounters for the primary care providers
Case

An 18 month old presents to the ER with a reported seizure that occurred at home, lasting 12 minutes. The seizure consisted of apnea with “tremulous shaking” of the all 4 limbs. On examination, the child is sleep but arousable. There are upgoing toes bilaterally but otherwise the examination is nonfocal. The parents deny illness but on taking a rectal temperature in the ER, it is found to be 39 C. What is this event most consistent with?

A. Simple febrile seizure
B. Complex febrile seizure
C. Likely the first manifestation of epilepsy, unmasked by fever
D. Dravet (SCN1A) syndrome
Febrile Seizures

- One of the most commonly encountered acute neurologic conditions in childhood
- NIH definition: “an event in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause.”
- ILAE definition: “seizure occurring in childhood after 1 month of age, 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 acute symptomatic seizures.”
Febrile Seizures

- Incidence is anywhere between 2-10% (depending on which study you look at)
- 90% of children have their first febrile seizure before the age of 3, with a peak between 18-24 months.
  - 6% occurred before 6 months of age
  - 4% occurred after 3 years of age
- Genetics plays a role in predisposition for febrile seizures.
  - 25-40% of children with febrile seizures have a family history
  - Should also prompt the neurologist to think about genetic epilepsies
    - GEFS+ (mutations in SCN1A, SCN2A, SNC1B, GABRG2)
- Pathophysiologic triggers have been implicated, but evidence is poor
  - Rate of fever rise
  - Peak body temperature
  - Vaccinations
Types of Febrile Seizures

- Simple FS (70-80% of FS)
  - Solitary event during illness
  - Nonfocal convulsion
  - Less than 15 minutes in duration

- Complex FS (20-30% of FS)
  - More than 1 event in 24 hour period (or same illness)
  - Focal symptomatology
  - Lasts longer than 15 minutes (includes febrile SE)
Case 1

The child is given Tylenol and within an hour returns to baseline. What work-up or evaluation does this child need in the setting of a FS?

A. Physical examination and potentially laboratory tests to evaluate for a source of fever
B. Routine EEG – could be done as an outpatient
C. MRI brain
D. Lumbar puncture
E. A & B
F. All of the above
Case 1

If this child had a complex febrile seizure, but appeared clinically the same following the event, what work-up would be indicated?

A. Physical examination and potentially laboratory tests to evaluate for source of fever
B. Routine EEG – could be done as an outpatient
C. Neurologic consultation
D. MRI Brain
E. Lumbar Puncture
F. A, B, and C
G. All of the above
Evaluation of Febrile Seizures

- Find and treat the cause of the fever (if applicable)
- Must rule out CNS infection and acute metabolic/toxic derangement
- A good H&P in addition to rapid/full postictal recovery in FS may establish the self-limiting nature of the febrile illness without need for further tests
- Lumbar Puncture?

<table>
<thead>
<tr>
<th>In Any Child Who Presents With a Seizure and Fever, a Lumbar Puncture:</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td>1a: Should be performed if the child has meningeal signs and symptoms or history or examination raises a possibility of meningitis or intracranial infection</td>
<td>B (Overwhelming evidence from observational studies)</td>
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<td>1b: Is an option in an infant 6–12 months of age when the child is considered deficient in <em>Haemophilus influenzae</em> type b (Hib) or <em>Streptococcus pneumoniae</em> immunizations or when immunization status cannot be determined</td>
<td>D (Expert opinion, case reports)</td>
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<td>1c: Is an option when the child has been pretreated with antibiotics, because antibiotic treatment can mask the signs and symptoms of meningitis</td>
<td>D (Reasoning from clinical experience, case series)</td>
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* Data from Subcommittee on Febrile Seizures; American Academy of Pediatrics, *Pediatrics.*
Evaluation of Febrile Seizures

- **Neuroimaging**
  - Not indicated unless clinical suspicion of an acute neurologic condition or a history of focal hemiconvulsions suggests a structural substrate.

- **EEG**
  - Of limited use in these cases as up to 1/3 of patients with FS (simple or complex) may show transient EEG abnormalities during the post-acute state
  - EEG alone seldom dictates management in FS
  - FEBSTAT study suggests that EEG may be beneficial in the setting of FSE as a marker of acute injury associated with FSE.
Counseling Families

- Mom: “I felt as if my child was dying”
- Dad: “I felt powerless to help…”
- It is important to clearly differentiate FS from epilepsy
Case 1

As you in the midst of counseling the family about the diagnosis, mom asks you: “Will this happen again?” What do you tell her?

A. It is very unlikely that this will ever happen again – only 5-10% of children have a second FS.
B. Yes, it is possible – about 1/3 of children with a first FS have a second FS
C. Yes, it is possible – about ½ of children with a first FS have a second FS
Counseling Families

• A second FS is likely to occur in 1/3 of patients
• A third FS is reported in ½ of the patients who have a second FS
• Only 15% of the entire cohort will have 3 FS
• <5% of a FS cohort will have >3 FS

• Recurrence Risk Factors
  • Age at the time of the first FS
    • The younger the age, the higher the risk, with potentially 50% recurrence risk in those younger than 1 year of age
  • History of FS in 1st degree relative
  • Low-grade fever during FS
  • Occurrence of the FS at the inception of fever/illness

• Not Risk Factors
  • Duration of febrile illness
  • Length of the 1st FS
Counseling Families

- Risk of epilepsy in the general population = 1%
- Risk of developing an unprovoked seizure after a FS = 2-5%
- Risk Factors for Future Dx of Epilepsy
  - Developmental delay
  - Abnormal neurologic examination
  - History of complex FS (including FSE)
  - First degree relative with epilepsy
- Longitudinal studies suggest that the risk of developmental, behavioral, and academic disability in children with FS is no greater than the general population
The distinction between epilepsy and febrile seizures is sometimes difficult and may require time as opposed to lab tests.
Case 1

As you prepare to send this patient home from the ER, the family asks about treatment for FS. What is your response

A. There is no treatments that we currently would advise

B. While we don’t encourage using anti-seizure medications, I can provide you with a prescription for rectal diazepam to administer for a convulsion that lasts longer than 3-4 minutes.

C. We will refer to neurology for consideration of starting an anti-seizure medication to reduce the risk of future FS

D. You should administer around the clock antipyretics when your child is sick to reduce the risk of recurrence.
Treatment of FS

- Antipyretics remain controversial in preventing FS but are generally recommended to help comfort the sick child
- Some studies have suggested benefit from intermittent benzodiazepenes during fever for preventing FS
  - 2-3 day course of oral diazepam
  - Not approved by the FDA and have side effects (sedation)
- Rectal diazepam for acute abortive treatment in FS recurrence
  - Earlier onset of effective treatment results in shorter total seizure duration
  - I consider this a must for children who have experienced an episode of FSE
- There is no justification for the use of daily anti-seizure medications
  - VPA and phenobarbital have been shown to reduce recurrence of FS but do not reduce ultimate risk of developing epilepsy
  - Long-term tx can be considered in a small subset of children with complex FS with multiple risk factors that portend a high risk of epilepsy
Case 2

A 6 month old little boy presents to you with concern for spells that began 2 weeks ago. Mom has recorded a spell. What is your next step?

A. Send the family home to see if they can suppress these spells. If they are able to suppress them by holding the child’s arms down, then you are less concerned.

B. Start a PPI as this is suspicious for GERD

C. Refer the child to see a pediatric neurologist

D. Send the child to the ER for emergent neurologic evaluation
Infantile Spasms

- West Syndrome
  - Infantile spasms + EEG findings + arrest/regression of development
  - The m/c epileptic encephalopathy – 1 per 2000-3000 infants
    - Typical onset is from 3-12 months of age
  - Flexor, extensor, or mixed spasms lasting 1-2 seconds in proximal/truncal muscles
    - Occur mainly in clusters and in sleep-to-wake transitions
    - May be asymmetric, symmetric, or unilateral
Case 2

On further examination, you are able to find several birthmarks utilizing a Wood’s lamp. These skin findings in addition to clinical events concerning for infantile spasms raises concern for which etiology?

A. Tuberous sclerosis
B. Neurofibromatosis, type 1
C. Vitiligo
D. Hypomelanosis of Ito
West Syndrome

• A clear etiology is evident in half of infants after exam/neuroimaging and in \( \frac{3}{4} \) following genetic/metabolic investigations.

• Structural etiologies are the most common
  • Cortical malformations
  • Tuberous sclerosis
  • Perinatal brain injury

• Genetic/metabolic etiologies can include:
  • Chromosomal abnormalities (Trisomy 21)
  • Mutations in several genes (CDKL5, STXBP1)
  • Pyridoxine dependency
EEG

- EEG = hypsarrhythmia (disorganized, paroxysmal, high voltage slowing with multifocal epileptiform discharges)

- May be on routine or may occur during non-REM only (need sleep recording)

- Disappears/reduces with REM sleep
Case 2

This child is given a diagnosis of West Syndrome, manifesting with infantile spasms, developmental arrest, and typical EEG findings. What is the treatment of choice?

A. Adrenocorticotropic hormone (ACTH)
B. Prednisolone
C. Vigabatrin
D. Ketogenic diet
E. Topiramate
Treatment of Infantile Spasms

- Vigabatrin is the treatment of choice in IS secondary to TS, with seizure cessation being seen in 95% of cases.
- ACTH has greater short-term efficacy once infants with TS are excluded.
- Studies have suggested similar short-term efficacy of ACTH and high-dose oral prednisolone – but currently there is insufficient evidence.
- Referral for surgical therapy is indicated in children with focal cortical structural abnormalities – particularly if hormonal treatment and vigabatrin fail to control spasms.
West Syndrome

• Most children with West syndrome have intellectual disability at follow-up and etiology is the most critical predictor of developmental outcomes
  • 50% of idiopathic cases have a normal/good outcome
  • 12.5% of children with symptomatic spasms have a good outcome
• Early treatment correlates with better long-term developmental outcome
  • ACTH/prednisone versus vigabatrin
  • VPA, TPM, ZNG, LEV, B6, ketogenic diet, combo therapies
  • The evidence is insufficient to recommend other therapies for treatment of infantile spasms (Level U)
Board Question

- You have a 6 month old baby with frequent extensor and flexor jerks that occur in the sleep-to-wake transition. His neurologic exam is otherwise unremarkable as is his skin exam. You hook him up to continuous EEG monitoring and this demonstrates hypsarrhythmia and electrodecrement associated with his spasms. His MRI is read as normal. What is his treatment of choice per recent AAN guidelines?

A. Low-dose ACTH (20-30 IU)
B. High-dose ACTH (150 IU/m²)
C. Prednisolone
D. Vigabatrin
E. Topiramate
West Syndrome

• *Neurology* 2012 *Practice Parameters*:
  - Low-dose ACTH should be considered
  - ACTH or vigabatrin may be useful for short-term treatment - ACTH is considered preferential
  - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference of vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome
Case 3

A 6 year old girl presents to you with staring spells. Parents describe these occurring several times daily to where they are unable to break him from the staring. They last 10-20 seconds and he appears fine afterwards. What would you expect to find on this child’s EEG?

A. 2.5 Hz slow-spike-wave discharges
B. 3 Hz spike-wave discharges
C. Paroxysmal fast activity
D. Normal EEG
Childhood Absence Epilepsy

- Accounts for 5-10% of all epilepsies in childhood
- Peaks at 5-7 years of age
- Neurologically normal children
- Typically the only seizure type is absence seizures
  - Brief (20-30 seconds or less)
  - Abrupt
  - Triggered by hyperventilation
- GTC seizures can develop in 30-40% of patients
Case 3

You send this patient for routine EEG. During hyperventilation, several absence seizures are provoked with a classic generalized 3 Hz spike-wave pattern. You refer to neurology but it may take 2-3 months for her to get an appointment. What do you prescribe?

A. Nothing, wait for the neurology appointment
B. Topiramate (Topamax)
C. Levetiracetam (Keppra)
D. Ethosuximide (Zarontin)
Treatment of CAE

• Ethosuximide is considered 1st line for treatment of CAE
  • Start at 15 mg/kg/day and increase to goal of 40 mg/kg/day (if needed)
  • Take with food

• Valproic acid and Lamotrigine are second line

• Focal seizure medications (carbamazepine/oxcarbazepine, vigabatrin) may exacerbate absence seizures
Case 3

Your 6 year old has been doing well on ethosuximide with no further absence seizures since starting. Unfortunately, you are notified that he presented to the ER after a first convulsive seizure – described as a generalized tonic-clonic. What is the best evidence-based choice of medication for this young man?

A. Start valproic acid and wean ethosuximide
B. Start valproic acid and keep ethosuximide
C. Increase the dose of ethosuximide
D. Start lamotrigine and wean ethosuximide
E. Start lamotrigine and keep ethosuximide
Case 4

You have an 8 year old young boy who presents to your clinic due to concern for seizures. His parents have found him at the floor of the bed several times in the past and he is unsure how he got there. On a few occasions they have found dried blood in his mouth from where he bit his cheek. Given this concern they moved him into their room and discovered him making strange sounds with his tongue and to have left sided-facial twitching. What does this most likely represent?

A. Benign rolandic epilepsy (aka benign epilepsy with centrotemporal spikes)
B. Panayiotopoulos syndrome
C. Electrical status epilepticus in slow sleep (ESES)
D. Juvenile myoclonic epilepsy
Benign Epilepsy with Centrotemporal Spikes (BECTS)

- One of the most common childhood epilepsies (6-10%)
- Peak age of presentation is 7-8 years of age
  - Resolves by 16 years old
  - Boys are more commonly affected
- Seizure appearance
  - Nocturnal seizures with perioral parasthesias, ipsilateral facial myoclonus, excessive salivation, speech arrest, guttural noises
  - This may then spread to hemiconvulsion or GTC
  - Seizures are usually brief, infrequent, and nocturnal
    - 10-20% have only a single seizure
    - Frequent seizures are seen in only 6%
- Postictal Todd paresis is seen in 7-16%, suggesting focal onset in those presenting with a “nocturnal GTC”
Benign Epilepsy with Centrotemporal Spikes (BECTS)

- EEG shows high amplitude centrotemporal spikes with activation during sleep
- Frequency, location, and persistence do not determine the clinical manifestations, severity, or frequency of seizures or prognosis
- Occur in 1% of normal school-aged children
  - Thus findings can be considered incidental if history does not support BECTS
- Spontaneously remit by 15-17 years of age
  - Typically within 2-4 years of onset
- Imaging is not required in a child with a normal neurologic examination and a classic history
Benign Epilepsy with Centrotemporal Spikes (BECTS)

- Anti-seizure medications may not be required for children with infrequent nocturnal focal seizures
- Recurrent seizures (if sufficiently disturbing to the child or family) may prompt treatment
  - Keppra
  - Oxcarbazepine
  - 50-65% will not have further seizures once a medication is started

- Prognosis
  - Remission occurs in all children
    - 50% remit by 6 years of age
    - 92% remit by 12 years of age
    - 99.8% remit by 18 years of age
  - Learning and behavior problems may be seen in the acute phase, long-term outcomes are excellent
Case 5

- 3 year old healthy boy preceding 2-week history of URI
- Presented to UVA ER with new-onset focal seizures, somnolence, slurred speech, ataxic gait, and urinary retention
- Neurologic consultation documented encephalopathy (lethargy and irritability), dysarthric speech, bilateral arm dysmetria and intention tremor, wide-based gait, whole body dysesthesias, and exaggerated deep tendon reflexes
- LP - lymphocytic pleocytosis (WBC = 64 cells/mL); normal protein and glucose. OCBs negative.
- MRI of the brain, cervical/thoracic spine
ADEM Diagnostic Criteria (2013)

- First polyfocal, clinical event of the CNS with presumed inflammatory demyelinating cause
- Encephalopathy (i.e., an alteration in consciousness or behavioral change) that cannot be explained by fever, systemic illness, or postictal symptoms
- Brain MRI is abnormal during the acute (3 month) phase with typical findings on brain MRI:
  - Diffuse, poorly-demarcated, large (12 cm) lesions involving predominantly the cerebral white matter
  - T1-hypointense lesions within the white matter are rare
  - Deep gray matter lesions can be present
- No new clinical and MRI findings emerge 3 months or more after the onset

Krupp LB et al. Mult Sclerosis 2013
Acute Disseminated Encephalomyelitis (ADEM)

- Immune-mediated disorder resulting in inflammatory demyelination of the brain and spinal cord.
  - Pre-pubertal children, the majority of which have a preceding febrile prodromal illness or immunization.
  - Encephalopathy with a rapidly progressive clinical course entailing multifocal neurologic dysfunction
    - Convulsive seizures occur in up to 35% of ADEM cases and may be a heralding feature
  - Mild-to-moderate CSF pleocytosis and elevated protein.
  - Oligoclonal bands are often absent in the CSF of patients with ADEM, but can be transiently noted in up to 10% of patients
- First-line therapy is high-dose IV corticosteroids
- ADEM is typically monophasic with the majority achieving full recovery
- Rarely, ADEM may be followed by other inflammatory disorders
Case

- Administered IVIg + high dose steroids with rapid improvement of his worsening symptoms.
- Within 2-3 months of discharge, patient had returned to his baseline functioning.
- Now 6 years old with no new events of demyelination and with normal development and cognition.
MOG-Associated Demyelination

- **Myelin Oligodendrocyte Glycoprotein**
  - MOG is a minor component of myelin structure, comprising 0.05% of total myelin proteins, and is exclusively expressed within the CNS.
  
  - Serum anti-MOG IgG detected in children with:
    - Monophasic ADEM
    - Neuromyelitis optica spectrum disorder (NMOSD)
    - Recurrent optic neuritis (ON)
    - Transverse myelitis (TM)

- Not all children with ADEM have detectable MOG antibodies; however, children with ADEM and anti-MOG IgG appear to exhibit a characteristic MRI pattern, nearly complete resolution of lesions, and better outcomes.

- MOG antibodies that rapidly and continuously decline after the acute phase of the disease appear to be supportive of a monophasic ADEM course

- MOG IgG argues strongly against a future diagnosis of MS

Hennes et al. Neurology 2017
MOG at UVA

• 3 year old boy developed a fever in early February 2018, and a few days into this febrile illness became excessively sleepy and had difficulty with walking and sitting up.
• Diagnosed with otitis media and started on antibiotics
• Continued to have poor oral intake, vomiting, and somnolence, and he presented to an outside ED on day 5 of illness, by which time the fever had resolved.
• CT head was normal and LP demonstrated 7 WBC's (lymphocytic), 2 RBC's, protein 26, and glucose 60.
• He received vancomycin, CTX, and acyclovir at the OSH
• Acyclovir was discontinued when HSV PCR returned negative in CSF.
• At UVA, MRI brain showed...
  • “Confluent, symmetric bilateral white matter restricted diffusion with associated non-enhancing T2/FLAIR signal abnormality.”
MOG at UVA

- Treated with IVIG 2 g/kg over 3 days and concurrent IV methylprednisolone 30 mg/kg daily x 3 days.
- Negative autoimmune encephalitis panel
- MOG antibody was positive (titer 1:100)
- Demonstrated rapid improvements in the days following IVIG/steroid treatment, and was discharged home with outpatient therapies.
- Back to baseline with no future relapses
“The soul is healed by being with children.”
— Dostoyevsky
References