Seizures in the Neonatal Period

When to suspect a seizure and what to do about it.

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Objectives

• Raise awareness of the factors that put a neonate at risk for a seizure.
• Describe and review examples of clinical and electrographic seizures.
• Describe options for treatment.
Outline

1. What puts a baby at risk for seizures?
   - Maternal
   - Fetal
   - Perinatal
   - Postnatal

2. What do seizures look like?
   - Clinical
   - Electrographic

Outline

   - Immediately
   - In the short term

4. Why does it matter if a baby has seizures?

Seizures in infants are COMPLICATED!

Difficult to identify

- In one study, only 9% of participants were able to identify an electrographic seizure with clinical observation alone.
- In another study, health care providers were shown videos of neonates with confirmed electrographic seizures. Only 50% of seizures were correctly identified.
Seizures in infants are COMPLICATED!

Difficult to treat

- It is known that anti-epileptics that are commonly used to treat neonatal seizures are only approximately 50 – 65% effective.
- Hypothermia is known to decrease the severity of seizures, but not suppress them.

Seizures - An Overview

- Approximately 1 - 5/1000 live births
- Defined clinically as abnormal stereotyped, paroxysmal alterations in neurological function - motor, behavioral, or autonomic
- Neonatal period has the greatest incidence of seizures
- Electrographically documented seizures may or may not have clinical manifestations

Seizures - An Overview

- Most common clinical manifestation of a neurologic insult during the neonatal period. “Seizures are almost always a symptom of a serious neurological problem. Treat the seizure, then start looking for the cause”;¹
- Most common cause of seizures is the term newborn is Hypoxic Ischemic Encephalopathy and Intraventricular Hemorrhage in the preterm infant.
Seizures - An Overview

• Early appearance of seizures and drug resistance to anti-epileptics are associated with poorer long term neurodevelopmental outcomes.
• Cannot predict which at-risk newborns will go on to have a seizure.

Seizures - An Overview

• EEG background is the most reliable indicator of which at-risk infants are most likely to suffer a seizure.
• Seizures will most likely occur between 12 and 48 hours of life
• Seizures in neonates are usually brief (5-10 seconds), focal and subtle.

Pathophysiology of Seizures

• “The immature brain is more susceptible to seizures because its GABA receptors have an excitatory effect, rather than the inhibitory effect seen with maturity”.1
• Seizures result from excessive synchronous electrical discharge “depolarization” in the CNS
• Depolarization is caused by the influx of sodium (Na+); repolarization is due to the outflow of (K+)
Pathophysiology of Seizures

Not completely understood why this depolarization occurs:

- Malfunction of the \( \text{Na}^+ \) (\( \text{K}^+ \)) pump?
- Excess of excitatory neurotransmitters?
- Deficiency of inhibitory neurotransmitters (GABA)?
- Ca and Mg inhibit Na movement?

Pathophysiology of Seizures

- Seizures consume ATP very quickly
- Brain glucose falls quickly (5 min in animals)
- Fall in glucose and rise in lactate lead to profound acidosis (from anaerobic metabolism)
- Repetitive seizures can cause:
  - Reduction in brain DNA
  - Impaired neuron differentiation
  - Impaired myelination

3 Reasons to Recognize and Treat Seizures

- Usually related to significant, underlying illness
- May cause further brain injury
- May interfere with supportive measures
  - Respiration
  - Alimentation
What puts a baby at risk for seizures?

**Maternal factors**
- Uncontrolled diabetes
- Placental abnormalities
- Drug use

**Fetal**
- Hypoxic Ischemic Encephalopathy (HIE)
  - Most common cause of seizures in newborns.
  - Definition: Abnormal neurologic behavior in the neonatal period arising as a result of a hypoxic-ischemic event.
  - Approximately 30% of infants with HIE go on to have seizures.
- Brain malformation/Structural malformation
  - 5-10%

**Inborn errors of metabolism**
- Pyridoxine Dependency (Vitamin B6)
- Transient metabolic deficits
  - Hypoglycemia
  - Hypocalcaemia
  - Hypomagnesaemia
  - Hyponatremia
What puts a baby at risk for seizures?

- Stroke
  - Ischemic
  - Hemorrhagic
    - Can be arterial or venous
- Infection of the CNS
  - 10%
  - Meningitis
  - Encephalitis
  - Intrauterine infection

Neonatal Epileptic Syndromes

- VERY RARE
  - Benign familial neonatal seizures
    - Onset is typically within the first week of life
    - Seizures are brief, lasting 1-2 minutes and frequent, up to 30 a day.
    - Babies display age-appropriate behavior in between seizures
    - Seizures typically cease after 6 months of age
    - Neurodevelopmental outcomes are normal

- Early Myoclonic Epilepsy
  - Characterized by intractable seizures that start in the first few days of life.
  - Babies appear severely encephalopathic
  - Associated with inborn errors of metabolism
  - Prognosis is extremely poor; most die within first year of life or suffer severe motor and cognitive disability

- Ohthara Syndrome
  - Differ from Myoclonic Epilepsy in that seizures are described as "tonic spasms"
  - Associated with structural malformation of the brain
  - Also a very poor prognosis; death likely within first year or lifelong severe cognitive and motor deficits
What puts a baby at risk for seizures?

Neonatal Epileptic Syndromes

Benign Neonatal Seizures (non-familial)
- Onset is typically within the first week of life
- Seizures are prolonged, repetitive and the infant technically fits the definition of being in status epilepticus.
- Seizures can last for as little as 2 hours and for as long as 3 days.
- Babies display age-appropriate behavior in between seizures
- Once seizures cease, they do not recur.
- Vast majority of neonates have normal neurodevelopmental outcomes

What do seizures look like?

Clinical
- There are four types of seizures
  - Subtle: Accounts for 50% of neonatal seizures
  - Clonic: 25%
  - Myoclonic: 20%
  - Tonic: 5%

  Subtle seizures are the most common type of neonatal seizure and are characterized by:
  - Eyes: Horizontal deviation of the eyes, with or without jerking, fixed stare, eyelid blinking or fluttering, eyes rolling up
  - Mouth: Sucking, smacking, chewing or tongue protrusions
  - Swimming or pedaling movements
  - Associated with HIE
What do seizures look like?

Subtle Seizures
- [https://www.youtube.com/watch?v=iM9j4qw7CA](https://www.youtube.com/watch?v=iM9j4qw7CA)
- [https://www.youtube.com/watch?v=8zAUF09j7mc](https://www.youtube.com/watch?v=8zAUF09j7mc)

What do seizures look like?

Clonic
- Multifocal: Rhythmic jerks of a limb which migrate to other limbs
- Focal: Rhythmic jerks localized to one limb
- Associated with stroke
- Occurs primarily in term neonates

What do seizures look like?

Clonic
- [https://www.youtube.com/watch?v=0j-pwZSKOpc](https://www.youtube.com/watch?v=0j-pwZSKOpc)
- [https://www.youtube.com/watch?v=8lA_omMsKf4](https://www.youtube.com/watch?v=8lA_omMsKf4)
What do seizures look like?

- **Myoclonic**
  - Rapid, single or arrhythmic repetitive jerks
  - Associated with severe brain damage and a poor prognosis
  - Associated with metabolic causes

- **Tonic**
  - Sustained contraction of the facial muscles and/or limbs
  - Extension of the limbs, mimicking decerbrate or decorticate posturing
  - Occur most often in preterm infants
  - Associated with a poor prognosis
What do seizures look like?

Tonic

- https://www.youtube.com/watch?v=nMbZWBPq_Ww
- https://www.youtube.com/watch?v=53OWcNb6nMQ

Seizures may be accompanied by changes in vital signs; most commonly, apnea with desaturation and tachycardia.

What do seizures look like?

Electrographic

- “a sudden, repetitive, evolving and stereotyped ictal pattern with a clear beginning, middle and ending and a minimum duration of 5-10 seconds.”

4
• Seizure reflected on raw and compressed tracing - beginning

• Seizure, raw tracing, middle

• Seizure, raw tracing, middle
• Seizure, raw tracing, ending
• Seizure, raw tracing, ended
Low voltage tracing with seizures
Subclinical seizure

Example of raw tracing 12 lead EEG
Status Epilepticus

- Generalized, convulsive SE in adults and older children refers to > 5 minutes of:
  - Continuous seizures or
  - Two or more discrete seizures between which there is incomplete recovery of consciousness
- A seizure does not have to last 5 min to be an emergency
### What is NOT a seizure?

<table>
<thead>
<tr>
<th>Jitteriness</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Sleep Myoclonus</td>
<td></td>
</tr>
<tr>
<td>Benign Non-Epileptic Myoclonus of Early Infancy</td>
<td></td>
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<tr>
<td>Hyperekplexia</td>
<td></td>
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<tr>
<td>EEG/aEEG artifact</td>
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</tbody>
</table>

### What is NOT a seizure?

**Jitteriness**

- Symmetrical tremor
- Can often effect all four limbs
- Stops with passive flexion
- Not associated with changes in VS
- Can be associated with hypoglycemia, hypocalcemia and drug withdrawal
- Normal EEG

### What is NOT a seizure?

**Benign Sleep Myoclonus**

- Occurs only during drowsy and sleep states
- Limb movements stop when awakened
- Mainly effects upper extremities
- Not associated with changes in VS
- Normal EEG
What is NOT a seizure?

Benign Non-Epileptic Myoclonus of Early Infancy
- “characterized by recurrent episodes of non-epileptic myoclonus while awake”\(^4\)
- Sudden, brief and symmetrical
- Occurs while awake
- Normal EEG
- Very rare in newborns – usually appears at approximately 4 mos

What is NOT a seizure?

Hyperekplexia
- Genetic
- Very, very rare
- Characterized by “excessive startle responses to unexpected auditory and tactile stimuli”\(^4\)
- In its severe form, baby becomes hypertonic and rigid following startle response and is susceptible to reparatory distress and apnea.

Artifact on the aEEG
Artifact on the raw aEEG (HFOV)

Another example of artifact on the aEEG
What do seizures look like?

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>More likely to be seizure</th>
<th>Less likely to be seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormality of gaze or eye movement</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Movements stimulus sensitive</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Predominant movement</td>
<td>Clonic jerking</td>
<td>Tremor</td>
</tr>
<tr>
<td>Movements cease with passive flexion</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Autonomic changes</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Body part(s)</td>
<td>Focal</td>
<td>Generalized</td>
</tr>
</tbody>
</table>

Seizure suspicion strong? Now what do you do?

- “The overall management goal for neonatal seizures is to quickly and accurately identify and abolish electrographic seizures, while determining the most likely underlying cause. A suspicion of seizures in a newborn should be treated as a neurologic emergency”. ¹

Acute management

- Glucose check
- Electrolyte check
- CBC, blood cultures and LP
- Video EEG/aEEG
  - EEG is considered the gold standard for seizure monitoring.
  - Although aEEG has its limitations, it’s far better than clinical observation alone.
  - In one study, recognition of seizures increased by 76% with aEEG and EEG.

Seizure suspicion strong? Now what do you do?

Acute management

• Consider passive or active hypothermia for HIE or stroke
• Anti-epileptic drugs
  - FIRST LINE
    o Lorazepam IV
    o Phenobarbital IV
    o Phenytoin and Fosphenytoin IV
  - SECOND LINE
    o Levetiracetam (Keppra) IV
    o Lidocaine IV
    o Midazolam IV
    o Topiramate PO
Seizure Rx

When depressed:
- Pharmacy is automatically called via Voalte
- Pharmacy calls back to confirm. It is heard via the intercom where the button was depressed and on the wall behind the bed. Please respond yes to pharmacy when they call back to confirm that you need seizure Rx (to R/O false alarm). They will come if you do not answer back.
- Fellow is also notified via Voalte at the same time as pharmacy

- Notify primary team
- Be prepared to give 1st line med (benzo) while waiting for pharmacy

Activating Touch Screen

Seizure Rx Button
The Anti-Epileptic Dilemma

• Do the benefits outweigh the risks??

Guiding principles for the use of AEDs
– Treat electrographic seizures with AEDs
– Decrease dose as soon as possible
– Discontinue dose as soon as possible.

Treatment with Phenobarbital
Seizure suspicion strong? Now what do you do?

**Short term**
- MRI
- Head Ultrasound
- Genetic labs
  - Serum amino acids
  - Ammonia
  - Very long chain fatty acids
  - Urine organic acids

**Differential Dx by Age**

<table>
<thead>
<tr>
<th>Day of Life 1-2</th>
<th>Day of Life 3-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH</td>
<td>ICH</td>
</tr>
<tr>
<td>Stroke</td>
<td>Inborn errors of metabolism</td>
</tr>
<tr>
<td>HIE</td>
<td>Intracranial infection</td>
</tr>
<tr>
<td>Hypoglycemia (early)</td>
<td>Drug withdrawal</td>
</tr>
<tr>
<td></td>
<td>Familiar epilepsy syndrome</td>
</tr>
</tbody>
</table>

**Differential Dx by Seizure Type**

- Subtle
  - HIE
- Clonic
  - Neonatal stroke
  - Preterm infants with severe ICH
- Tonic
  - Structural brain abnormalities
- Myoclonic
  - Metabolic causes
Why does it matter if a baby has seizures?

- Seizures are known to interfere with brain development and can lead to deficits in learning, memory, behavior, and motor ability.
- Seizures in the neonatal period are associated with early death.
- For those that survive, many will have mild – severe motor and cognitive disabilities, which varies depending on the extent of injury.

Case Study #1

- Maternal History
  - Hypertension with superimposed pre-eclampsia
  - yeast vaginitis
  - GDMA2
  - HIV positive (viral load undetectable)
  - h/o HSV without active lesions at time of discharge
  - Depression

- Labor & Delivery
  - NSVD to clear fluid
  - 2590 grams
  - Peds called to delivery for apnea at one minute of life. Baby blue and floppy without spontaneous respirations. PPV initiated x5 minutes. After 5 minutes, baby began to have some spontaneous respirations. PPV was stopped and CPAP initiated. HR was above 100 throughout resuscitation course.
  - Apgars 3/7/7
Case Study #1

- NICU Course
  - Baby was transferred to the ICN due to need for need for increased respiratory support and decreased tone/encephalopathy.
  - Baby’s initial blood glucose was 14. After a D10 bolus, baby’s blood glucose improved to 48.
  - However, the baby’s neuro exam did not improve significantly (decreased tone, encephalopathy).
  - ABG: 7.14/24/66/-20
  - Cooling initiated

Case Study #1

- A CFM monitor and full EEG were placed on admission. On 12/23, 3 events were noted to be consistent with subclinical seizure, and so phenobarbital treatment was started.
- The baby had an initial coagulopathy with elevated INR and PTT, requiring 3 FFP infusions and Vitamin K for 3 days.
- NS boluses for hypotension. Dopamine was initiated.
- A HUS was performed on 12/23 and was normal.

Case Study #1

- On DOL 2, desaturation + bradycardia requiring intubation. Remained intubated until rewarming. She was extubated to room air on 12/26.
- An MRI was performed on 12/27/2012 (5 days old) showed evidence of older resolving hemorrhage as well as watershed infarcts in the PCA and MCA distribution of her occipital lobe, left greater than right, consistent with moderate injury.
- On further review of the infant’s course by the consulting Neurologists, it was thought that all seizure episodes on CFM were artifactual and she never had evidence of clinical or subclinical seizures.
Case Study #1

- Feeds were initiated on 12/26. She has had difficulty taking sufficient oral feeds after recovery from her initial insult, and so a Gastrostomy-tube was placed on 1/24.

  • Follow-Up
    - 6/13/2013
      - Purposeful motor activity increasing.
      - Becoming more verbal
      - Taking most pureed foods orally and has improved sucking effectiveness. G-tube use is now limited to night time continuous feeds.
      - Muscle weakness is greater on right upper extremity but improving. Still has some truncal weakness.

• 4/24/2014
  - Left sided paresis. Responding to therapy as evidenced by using left hand more and walking has become less clumsy.
  - Expressive language is still delayed.
  - Feedings: Oral intake is improving. Still has gastrostomy tube in place.

  • 8/28/15
    - progressing well developmentally

• 1/17/16
  - G-tube was removed 9/15
  - Trouble swallowing
  - Speech difficulty (mild lisp) and weakness.

  • 1/5/17
    - Umbilical hernia
    - Some difficulty with articulation of words
    - Otherwise, developmentally normal
Case Study #2

Maternal History
• 38-year-old G2P1-2 with late transfer of care to the United States from Mexico
• Good prenatal care and uncomplicated pregnancy
• Family history is significant for older son with cognitive delay and musculoskeletal issues requiring physical/occupational therapy.

Labor & Delivery
• 38 weeks at San Joaquin Hospital

Case Study #2

Mother presented to San Joaquin Hospital on 12/10/12 with complaints of decreased fetal movement for 1-2 days.
• NRHFT urgent C-section.
• Meconium & tight nuchal cord x2.
• Cyanosis with poor respiratory effort and HR between 60 and 100 bpm.
• PPV x 2 minutes, then baby began to cry, but had retractions.
• Apgars 4/7/7
• Birth weight: 2170 gm

Case Study #2

NICU Course
• Patient was placed on CPAP, then intubated for apnea.
• Glucose = 27, started on IV fluids.
• Patient’s first blood gas was pH 7.1, pCO2 60, pO2 32, HCO3 18, and BD -13.
• Transferred to UCSF for TH
Case Study #2

NICU Course UCSF

- Patient was placed on mechanical ventilation for transport. After arrival at UCSF, ventilator settings were weaned quickly due to hypocarbia, and he was placed on CPAP via ET tube.
- Neurologic exam was notable for mildly increased tone in extremities, mildly decreased axial tone, and no gag; patient opened eyes spontaneously, withdrew to pain, and had normal deep tendon reflexes.
- Patient was placed on a/EEG.

- At approximately 3 am on 12/11/12 was noted to have seizure activity on EEG corresponding with bilateral eye-jerking, including one 8-minute seizure. He was given lorazepam and then loaded with phenobarbital, with cessation of seizures. At approximately 2 pm on the same day, he had recurrence of seizure activity on EEG and was re-loaded with phenobarbital and started on maintenance dosing.
- He had no further seizures, but continued to have markedly abnormal neurologic exam with decreased upper extremity tone, increased lower extremity tone, poor suck and gag, and minimal spontaneous eye opening.
- EEG background of persistent burst suppression.

- Patient had hypotension requiring dopamine on 12/11/12.
- Patient received fresh frozen plasma transfusion on 12/11/12 for volume resuscitation and INR 1.5.
- On 12/12/12, brain MRI showed extensive bilateral watershed territory cerebral infarction, consistent with severe hypoxic ischemic injury.
Case Study #2

- Given the severity of brain injury, recommended redirection of care.
- Prognosis with the type of injury observed combined with the poor neurologic exam and EEG background of persistent burst suppression, even after completing cooling, was anticipated to be very poor with quadraparesis, probably blindness, inability to feed or care for self and impaired cognition.

Case Study #3

Maternal History

- The pregnancy was complicated by:
  - obesity (pre-pregnancy BMI 30),
  - hyperemesis
  - poor fetal growth; growth curve dropped from the 30th percentile to ≤10th percentile during the 3rd trimester
  - pregnancy-induced hypertension
  - doppler studies and biweekly non-stress tests were done and were reassuring.
  - Pregnancy loss of twins at 19 weeks in 2002.

Labor & Delivery

- SROM~26 hours prior to delivery.
- The amniotic fluid was clear.
- The mother’s blood pressure was elevated; started on magnesium sulfate for seizure prophylaxis.
- NSVD
- Terminal meconium
Case Study #3

- Infant was born limp with no respiratory effort. The infant's mouth and nose were suctioned and bag/mask ventilation was initiated at 1 minute of life when the heart rate dropped below 100 beats per minute.
- The infant responded well to the bag/mask ventilation and after a few minutes was transitioned to mask CPAP when she began initiating some breaths.

Case Study #3

NICU Course

- NCPAP of 5, FiO2 30%.
- Her VS remained stable until ~ 6 hours of life at which time she began having apnea.
- Dopamine started and NS boluses for a lactate of 11.
- On admission, the infant was noted to be hypotonic and sleepy. A limited neurologic exam was otherwise grossly normal, and her hypotonia and sleepiness were suspected to be due to the magnesium sulfate that the mother was on at the time of delivery.

Case Study #3

- ABG: 7.29/31/92/-11
- Did NOT meet the criteria for cooling
- Baby intubated on 12/29/2012 at ~ 17 hours of life after persistent episodes of apnea.
- aEEG was placed after apnea that required intubation.
- At ~11 hours of age, the infant's CFM tracing was consistent with status epilepticus. A full montage EEG confirmed the CFM findings. The seizure activity was subclinical in nature, and extremely difficult to control. She ultimately required 3 anti-seizure agents, including Phenobarbital, Fosphenytoin, and Keppra to stop the seizure activity.
Case Study #3

- **Neuro Exam at 20 HOL:**
  - Minimal responsiveness
  - No track or fix
  - No suck or gag
  - Hypotonia
  - No deep tendon reflexes

- **Neuro Differential Diagnosis**
  - Acute HIE
  - Infection
  - Magnesium toxicity
  - Metabolic disorder

The infant underwent several imaging studies of her brain. A head ultrasound on 12/30/2012 showed no intraventricular hemorrhage, but was significant for slit-like ventricles with minimal CSF due to diffuse cerebral edema. A repeat head ultrasound on 1/1/2013 showed a stable appearance of the cerebral edema, as well as new diffuse white matter hyperechogenicity.

A brain MRI on 12/31/2012 showed global injury with diffusely reduced diffusion, diffuse cerebral edema and uncal herniation, with a moderate lactate peak on spectroscopy which is consistent with a metabolic or mitochondrial defect as opposed to hypoxic ischemic encephalopathy or infection.

A follow up MRI was performed on 2/12/2013 which showed profound cystic encephalomalacia in areas of previous ischemia with white matter affected greater than grey matter.

An EEG 2/11/2013 showed low-amplitude, featureless background indicating global cerebral dysfunction, frequent right frontal spike-wave discharges, indicating epileptic potential of this region. There were no electrographic seizures.
Case Study #3

- Regardless of the underlying mechanism of disease, this infant has experienced devastating and irreversible brain damage with near complete obliteration of the entire neocortex white matter. Per Neurology, it is doubtful whether the infant will ever exhibit volitional behaviors. Given the damage already manifested, coupled with the diagnoses under consideration, continued brain degeneration and death within the first few years of life is likely.

Case Study #3

- Early in the infant’s hospital course, the parents were offered re-direction of care to comfort care, but they ultimately decided to proceed with life-saving measures. While the parents are realistic about the difficulties that their child will likely face, they were dedicated to providing the necessary care to allow their daughter to thrive to the best of her ability.
- Baby initially fed via NG, then transitioned to PO.
- Could not PO all feeds, so GT placed 2/8
- Transitioned to RA early in hospital course
- DC’d 2/19/13

Case Study #3

Follow-Up
- As of 3/15/13, still no identified cause of her brain abnormalities
- 4/22/13: Seen in epilepsy clinic for return of seizure activity
- 10/28/13: Diagnosis:
  - 1) Severe psychomotor delay
  - 2) Spastic quadriplegia
  - Free interval of seizures for a few months, then occurrence of infantile spasms successfully treated with steroids. She currently has daily brief (10-20 seconds) focal seizures with bilateral tonic abduction of both arm and head and eye deviation to the right.

-
Case Study #3

3/21/16
- Fussy but not always
- seems to enjoy movement, music
- has smiled and laughed a few times with kinetic play
- no purposeful movements
- no oral intake or interest

8/9/17
- admitted to the hospital 4 times in June and July for illness, worsened seizures, fussiness
- clear sense she is calmer at the hospital, more fussy at home-feel some of this is overstimulation at home with a busy household
- EEG last visit shows very active, lots of seizures, also events that were concerning but are not seizures
- WES back, wnl, no mutations to explain her neonatal MRI changes

References