Neonatal Seizures

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Seizures

- The most frequent manifestations of neonatal neurologic disease

No disclosures

- I think I saw a seizure once (I may have been wrong)

- Special thanks to:
  - Robert Clancy, MD
  - Joshua Hite, Pharm D

Objectives

THE QUESTIONS

- Discuss the difficulty in diagnosing neonatal seizures (NS)
- Discuss treating NS as a standard of care to improve long-term outcomes
- Review the most common medications used to treat NS

THE ANSWERS

- It’s hard, you need to be monitoring the brain
- Electrographic NS should be treated, especially if they are of long duration
- Phenobarbital, Keppra, Phenytoin

Neonatal seizures (NS)

- Seizures occur more frequently in the neonatal period than at any other period during life
- Most common cause of NS is Hypoxic-ischemic encephalopathy (HIE)
- Benign forms include:
  - Benign familial neonatal seizures & transient, treatable metabolic derangements
  - These forms of neonatal seizures are largely without significant long-term consequences
- In the past, controversy existed as to whether the seizures themselves caused damage to the immature brain (or if the brain injury was primarily due to the underlying cause of the seizures)
- Most experts now believe seizures themselves can cause brain injury
- Some infants with NS do well
- NS can be a sign of a neurologic disorder and associated with long-term neurologic sequelae
- Cerebral palsy, cognitive and developmental delays, and later epilepsy

Definition of seizure

- For parents – “abnormal electrical activity in the brain”
- Physiologic – excessive, synchronized depolarization by a large group of neurons
- Clinical – a paroxysmal alteration in neurologic function (manifests in many ways -- jerking, stiffness, convulsions, other unusual paroxysmal events)
- Electrographic seizure
  - A sudden, repetitive, evolving, and stereotyped ictal pattern with a clear beginning, middle, and ending and minimum duration of 10 seconds
Electrical seizure activity begins in the midline central region (CZ) and then shifts to the left central region (C3). Toward the end of the seizures, as the electrical activity persists in the left central region, the midline central region becomes uninvolved. This electrical seizure activity occurred in the absence of any clinical seizure activity in this 40-week gestational age female infant with hypoxic-ischemic encephalopathy. She was initially comatose and hypotonic and, at the time of EEG recording, had been treated with phenobarbital.

### Classification of NS

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
<th>EEG Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtle</td>
<td>Ocular, oral-buccolingual, autonomic, apnea, limb posturing and movements</td>
<td>Variable</td>
</tr>
<tr>
<td>Clonic</td>
<td>Repetitive jerking, distinct from jittering, Unifocal or multifocal</td>
<td>Common</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>Rapid isolated jerks, Focal, multifocal or generalized</td>
<td>Common if generalized, Uncommon if focal</td>
</tr>
<tr>
<td>Tonic</td>
<td>Stiffening, Decerebrate posturing, Focal or generalized</td>
<td>Common if focal, uncommon if generalized</td>
</tr>
</tbody>
</table>

Subtle NS

- Subtle seizures are the most common seizure type in both preterm and term babies.
- May present as:
  - Ocular phenomena (staring, blinking, eye deviation, eye opening)
  - Oral phenomena (mouthing, chewing, sucking, smiling)
  - Autonomic phenomena (change in blood pressure and/or heart rate, pallor, increased)
  - Salivation or secretions
  - Central apnea occurring rarely as the only seizure manifestation
  - Fragmentary body movements (limb posturing, swimming, pedaling)

Jitteriness Does NOT = seizures

- Movements cease on application of passive flexion
- Movements are stimulus sensitive
- Predominant movement is tremor

Neonatal seizures (NS)

- Risk of seizures is highest during the lifespan during the neonatal period
- Occur in 1.5–5/1000 live births
  - 2-3/1000 term newborns
  - 10-15/1000 preterm infants
  - Often due to perinatal asphyxia or IVH
- Often are:
  - Brief
  - Recurrent
  - Subclinical
  - Focal

- Compared to seizures at older ages in life...
  - Different causes
  - Different signs
  - Different EEG signature
  - More refractory to antiepileptic drugs (AEDs)

The immature brain is prone to seizures

- More prone to seizures than adult brain
- Newborns have an imbalance between maturation of excitatory and inhibitory circuits, favoring excitation
- GABA (the main inhibitory transmitter in adults) system has delayed maturation in the immature brain
- Excitatory networks develop before inhibitory networks
- Allows for plasticity and learning (good)
- Places the infant at high risk for seizures (bad)
Imbalance of excitatory (glutamate) and inhibitory (GABA) neurotransmitter receptors in favor of excitation
Promotes synapse formation, plasticity, remodeling = good
Allows for lower threshold for seizures = bad


**Temporal Profile of Individual EEG Seizures: NOT Bimodal!**

Most neonatal seizures last < 2 min


**Conventional Definition of Status Epilepticus**

Status-NO

+ 2 mins 2 to <3 mins 5 to >10 mins >30 mins

Status-YES

!!!

**Distribution of EEG Seizure Burden: NOT Bimodal!**

Distribution of Seizure Burden Values (N=125 EEG Recordings)

Convenience sample of 851 Szs in 125 neonatal EEGs (23-145 minutes); SE in 18/125 (14%)


**Etiologies of Neonatal Seizures**


What is status epilepticus (SE) in the newborn?

- No accepted consensus for definition of SE
- Traditional definitions don’t apply:
  - 30 minutes of continuous EEG seizure
  - Serial seizures without return of awareness between seizures
  - CHOP operational definition: continuous 30 mins or ≥ 50% of EEG with electrographic NS
  - Dr. Clancy estimates ~ 1/4 to 1/3 of neonates with EEG confirmed seizures may have ≥50% ictal EEG seizure activity (are in status)

“Idiopathic” = rare, so find the etiology of the seizure.
The etiology of the seizure is most important determinant of outcome.
HIE and NS

- **HIE** = most common cause of neonatal seizures.
- Causes ~2/3 of cases of neonatal seizures.
- HIE affects 1-2/1000 live births.
- Seizures occur usually within the first 1-2 days after birth, then remit.
- 40-60% of patients with HIE develop seizures.
- With HIE, seizures carry with them a risk of long-term epilepsy and neurologic or cognitive deficits.

Causes of NS

- 2nd most common cause of NS = cerebrovascular disorders
  - Arterial and venous stroke
    - Most have no evidence of coagulopathy
    - Most have low risk of stroke recurrence
  - Intracerebral hemorrhage
  - Subarachnoid hemorrhage
- 3rd = infectious causes and malformations of cortical development
  - Bacterial: commonly GBS and E. Coli
  - Nonbacterial: Toxoplasmosis, CMV, HSV coxsackie
  - CNS malformations: lissencephaly, polymicrogyria, focal cortical dysplasia and tuberous sclerosis

Causes of NS

- Metabolic disturbances: hypoglycemia, hypocalcemia, hypomagnesemia, abnormalities of other electrolytes and amino acids
  - Often these causes are treatable
  - Rarely associated with significant long-term consequences if they are the primary cause of NS
- Pyridoxine-dependent seizures
  - Can present as unremitting, refractory seizures within the 1st days of life
  - Rapidly respond to IV pyridoxine
  - Inborn errors of metabolism

Causes of NS

- Benign familial neonatal convulsions
  - Autosomal dominant disorder
  - Presents within the 1st week of life
  - Subsequent normal development
  - Due to mutations in neuronal potassium channels
- Infants with congenital heart disease are at higher risk of seizure

Diagnosis of NS

Risk factors for neonatal seizures

- Family history – epilepsy
- Pregnancy history
  - TORCH infections
  - Known CNS malformation
  - Known chromosomal/genetic disorder
  - Fetal narcotic exposure
  - Abnormal growth, abnormal fetal movements/muscles – could be due to neurologic abnormality
- Delivery history
  - Preterm delivery...JWH?
  - Emergent delivery...HIE?
  - Postnatal course
  - Unusual movements
  - Apnea/desaturations
  - Blood pressure instability
  - Known infections...meningitis
  - Known electrolyte disturbances
Diagnostic work-up

- Labs
  - CBC, blood culture, CRP
  - Glucose, electrolytes
  - Ca++, Mg++, pH (blood gas)
  - Urine CMV
  - Chromosomes/Microarray
    - Especially if other work-up is unrevealing
- Lumbar puncture
- EEG/aEEG or "CFM"
- Neuroimaging – Cranial US, CT, MRI
  - Be aware of radiation exposure with CT
- Therapeutic trial of pyridoxine, pyridoxal-5-phosphate, or folic acid

Treat the cause of the seizures in addition to the seizures themselves.

Diagnosis

- Clinical diagnosis
  - Based on clinical observation of unusual paroxysmal events
  - Does NOT require EEG confirmation
- EEG diagnosis
  - Requires an ictal discharge on EEG
  - EEG ictal discharge may or may not correlate with the unusual event
  - Interictal EEGs may be normal!

Benign sleep myoclonus

- First described in 1982 by Coulter and Allen
- A disorder commonly mistaken for seizures during the newborn period.
- Characterized by myoclonic "lightning like" jerks of the extremities that exclusively occur during sleep
- Waking the child should eliminate the symptoms
- Not correlated with epilepsy
- Often prompts hospital admission and extensive diagnostic testing, including neurophysiologic studies, brain imaging, and screening for infection
- Resolves without sequelae

Why can’t we use the clinical definition?

http://www.youtube.com/watch?v=6uyqAkQdp

Electrographic seizures are very under-recognized by clinical observation alone

NCS="no clinical signs"; CS=definite clinical signs
393 electrographic seizures in 41 neonates

(Clancy, Legido & Lewis Epilepsia 1988; 29: 256)
“EEG is essential for the diagnosis and for assessing treatment efficacy...”

A substantial proportion of EEG seizures are not recognized by clinical observation alone

Amplitude-integrated EEG (aEEG) or “Cerebral function monitor” (CFM)
- Monitors general neurological status
- Seizure detection
  - Detects ~75% of neonatal seizures (compared to conventional EEG)
  - Can help detect “clinically silent” (subclinical) seizures
  - Can miss seizures - especially, if they are short, of low amplitude or migrating from one channel to another.
- Monitors drug effects and therapies
- Assists in assessing need for full EEG
Amplitude integrated EEG

One Channel

FP1-T3
T3-O1

FP2-T4
T4-O2

FP1-C3
C3-O1

FP2-C4
C4-O2

T3-C3
C3-CZ
CZ-C4
C4-T4

C3-C4

Comment
75 uV
2 sec

CFM – Pattern recognition

- Normal
- Seizures

CFM – Pattern recognition

- Normal
- Moderately abnormal

CFM – Pattern recognition

- Normal
- Severely abnormal

Sensitivity of aEEG to detect electrographic seizures

C₃→C₄ simulates P₃→P₄ for aEEG channel

Amplitude integrated EEG

normal sample of a-EEG (one channel: C₁→C₄)

Sensitivity of aEEG to detect electrographic seizures

Amplitude integrated EEG normal sample of a-EEG (one channel: C₁→C₄)

Seizure at Fp₁ not seen in C₃→C₄

Seizures in tiny premies may be of very low frequency and possibly filtered out by aEEG making access to the raw EEG trace and/or seizure detection algorithms valuable for seizure detection.

Conventional EEG (cEEG) vs. aEEG

- cEEG is the “gold standard” for seizure detection:
  - Exact number, duration and locations
  - Recorded continuously but read intermittently
  - Applied by technologists and interpreted by neurophysiologists
  - Difficult to trend background
  - $$$

- CFMs such as aEEG relatively insensitive to seizures (but better than no EEG)
  - May miss short, infrequent, localized seizures (which are common in neonates)
  - Recorded continuously and read at bedside PRN
  - Real-time interpretation
  - Applied and read by bedside caregivers
  - Simple compressed display of background over time
  - $$

Do we need to treat NS?

What are the long term outcomes of seizures in the neonate?
Outcomes of prolonged NS

- Outcome of prolonged NS in survivors can include long-term problems in > 30% of survivors
- Consequences in survivors:
  - Learning disability - 27%
  - Developmental delay and mental retardation - 20%
  - Epilepsy later in life - 27%
  - Mortality - < 20%
- Worst prognosis: seizures caused by HIE or cerebral dysgenesis
- Better prognosis: milder EEG abnormalities and no neuroimaging abnormalities


Chronic epilepsy after neonatal seizures

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients with epilepsy</th>
<th>Infants with neonatal seizures</th>
<th>% with epilepsy after neonatal seizures</th>
</tr>
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<tbody>
<tr>
<td>McInerny, 1969</td>
<td>8</td>
<td>52</td>
<td>15</td>
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<tr>
<td>Rose, 1970</td>
<td>29</td>
<td>110</td>
<td>26</td>
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<td>Drinnan, 1990</td>
<td>18</td>
<td>214</td>
<td>18</td>
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<tr>
<td>Bergman, 1990</td>
<td>24</td>
<td>250</td>
<td>20</td>
</tr>
<tr>
<td>Frijns, 1991</td>
<td>28</td>
<td>317</td>
<td>18</td>
</tr>
<tr>
<td>Mizrahi &amp; Clancy, 2001</td>
<td>32</td>
<td>121</td>
<td>26</td>
</tr>
<tr>
<td>Pisani, 2007</td>
<td>22</td>
<td>106</td>
<td>21</td>
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</tbody>
</table>


Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial

Neo HIE randomized to clinical seizure management versus aEEG based management

Seizure duration

<table>
<thead>
<tr>
<th>MRI injury</th>
<th>aEEG</th>
<th>No aEEG</th>
</tr>
</thead>
</table>


Cooling for HIE

- Therapeutic hypothermia is the standard of care for infants with moderate to severe HIE > 35-36 weeks EGA
- Shown to improve outcome
- Number needed to treat ~ 6-7
- 40-60% of patients with HIE develop seizures
- NS may be difficult to control in these patients
- Hypothermia may decrease seizure burden in these infants


Medications for the treatment of NS

- Anti-convulsants
- Anti-epileptic drugs (AEDs)
- Anti-seizure drugs (ASDs)
- None are FDA approved for neonates in the U.S.
- AEDs may just cause electroclinical uncoupling or dissociation without terminating the seizure
- AEDs have limited efficacy in the neonate
- AEDs may actually cause harm: Phenobarbital and phenytoin may promote apoptosis in the developing brain

Don’t forget to treat the underlying cause of the seizure!


Phenobarbital

- Class: antiepileptic, barbiturate
- Mechanism of action: Increased synaptic inhibition
  - Potentiates GABA-ergic neuronal transmission by increasing the duration of Cl- channel openings leading to membrane hyperpolarization and decreasing excitability
  - Also can suppress the reticular activating system leading to sedation, amnesia, loss of consciousness
- Available routes: IV, IM, PO, PR
Phenobarbital

- Loading dose: 20 mg/kg
  - Refractory seizures: can give additional 5 mg/kg doses up to 40 mg/kg total
- Maintenance dose: 3-4 mg/kg per day beginning 12-24 hours after the load
- Target drug level: 15-40 mcg/ml
- Side effects: sedation, respiratory depression (lethal at high doses)
- Metabolized by the liver (induction of hepatic P450 system)
- Serum half-life in neonates is 40-200 hours (can accumulate even at maintenance dosing during the first 2 weeks of life)

Phenytoin (Dilantin)

- Traditionally the most widely used 2nd line drug (has been overtaken by Keppra in the last decade)
- Class: antiepileptic
- Mechanism of action: Inhibits generation of high-frequency repetitive action potentials by binding to neuronal Na+ channels (prolongs the refractory period)
  - Limits the spread of seizure activity and reduces seizure propagation
- Available routes: PO (poor bioavailability)
- Often given as the prodrug fosphenytoin
- Can be given IV

Phenytoin (Dilantin)

- Loading dose: 15-20 mg/kg
- Maintenance dose: 4-8 mg/kg per day
- Target drug level: 6-15 mcg/ml in the 1st few weeks of life, then 10-20 mcg/ml
- Side effects
  - Toxicity: nystagmus, diplopia, ataxia, sedation
  - Gingival hyperplasia and hirsutism with long-term use
  - Teratogenic: "fetal hydantoin syndrome"
- Metabolism by the liver is limited and can lead to drug accumulation
- Half-life is 18-60 hours
- Exhibits cross reactivity at cardiac Na+ channels & can be used as a class IB anti-arrhythmic
  - Monitor for hypotension, bradycardia, arrhythmia during infusion

How effective is standard (phenobarbital or dilantin) for treatment of neonatal seizures?

- Phenobarbital 1st: 13 of 30 = 45% had seizures controlled
- Dilantin added: 57%
- Phenobarbital added: 62%

- About the same efficacy; neither is very good alone (<50%), together still missing ~ 40% of seizures

Painter et. al., NEJM 1999.
Lorazepam (Ativan)

- Usually a 2nd or 3rd line agent
- Class: benzodiazepine
- Mechanism of action:
  - Binds to the benzodiazepine site on the GABA receptor complex (GABA receptor agonist)
  - Increases the frequency of Cl channel openings leading to membrane hyperpolarization and decreased excitability of neurons
  - Depresses all levels of the CNS (including the limbic and reticular formation)
- Available routes: usually IV for seizures, PR

- Dose: 0.05 to 0.1 mg/kg, repeat doses based on clinical response
- Onset of action within 5 minutes, peak concentrations reached by 45 minutes
- Metabolized in the liver, renally excreted
- Duration of action: 3 to 24 hours, mean half-life in term infants of 40 hours

Levetiracetam (Keppra)

- Now 2nd most commonly used AED in neonates
- Use has increased ten fold over the last decade
- FDA approved for children > 1 month of age
- Mechanism of action: inhibits burst firing without affecting normal neuronal excitability, suggesting selective prevention of hypersynchronization of epileptiform burst firing and propagation of seizure activity
- Not utilized for status epilepticus treatment due to delay in action
- Route: IV, PO

- Initial dose: 10 mg/kg daily
- Maintenance: Adjust dose upwards in 1 to 2 week intervals to max of 30 mg/kg per dose
- Trough concentrations are not routinely monitored
- No known significant drug interactions
- Onset of action within 30 minutes with peak concentrations within 2 hours
- Half-life in neonates ranges within 18 hours
- Wide safety margin

Other AEDs for NS

- Concerns about cardiac toxicity have limited widespread use of lidocaine
  - Risk of arrhythmia; should only be given in a NICU setting and with continuous cardiac monitoring
  - Discontinue immediately if arrhythmia occurs
  - Avoid in newborns with congenital heart disease

- In Europe midazolam and lidocaine are used more commonly than in the U.S. typically as 2nd/3rd line agents
- Efficacy of midazolam varies widely

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- Efficacy of midazolam varies widely
AEDs with ongoing trials

- Keppra – 2 studies comparing it to phenobarbital as a 1st line AED
- Bumetanide – 2 clinical dose finding studies
  - A loop diuretic
  - Blocks the sodium/potassium/chloride (NKCC1) co-transporter that is highly expressed in immature neurons
  - Results in GABA-mediated inhibition
- Topiramate – 2 trials looking at neuroprotection in HIE
  - Reduces the frequency of action potentials during sustained depolarization and may have neuroprotective properties


References

- Clancy MG, Ungopp A. The role of status epilepticus and clinical seizures as a marker for neonatal encephalopathy. Epilepsy. 2010 Feb;51(2):166-71.

Which AEDs are currently being used in the U.S.?

- From 2005 to 2014, 934 infants from 341 facilities with a seizure diagnosis and who received an AED were analyzed
- Most commonly used agents overall
  - Phenobarbital (96%) – comparison with phenytoin for the treatment of neonatal seizures. Epilepsia. 1999 Aug;40(suppl 7):S51-62
- Keppra (14%) – comparison with phenytoin for the treatment of neonatal seizures. Epilepsia. 1999 Aug;40(suppl 7):S42-4
- Bumetanide (11%) - no randomized trials have been performed to answer this question and no consensus exists on treatment duration
- Patients should be referred and followed by a pediatric neurologist
- Most common single AED
  - Phenobarbital, followed by Keppra
- Most common combination therapy order
  - Phenobarbital, then Keppra (49%) – comparison with phenytoin for the treatment of neonatal seizures. Epilepsia. 1999 Aug;40(suppl 7):S42-4
- Phenobarbital, followed by Keppra
  - Phenobarbital, then phenytoin (36%) – comparison with phenytoin for the treatment of neonatal seizures. Epilepsia. 1999 Aug;40(suppl 7):S42-4


References

- Clancy MG, Ungopp A. The role of status epilepticus and clinical seizures as a marker for neonatal encephalopathy. Epilepsy. 2010 Feb;51(2):166-71.

How long should NS be treated?

- No randomized trials have been performed to answer this question and no consensus exists on treatment duration
- Patients should be referred and followed by a pediatric neurologist
- Durations of treatment seem to be getting shorter given
  - The potentially toxic effect of AEDs on brain development
  - Knowledge that most NS are controlled within a few days of medication initiation
- Historically AEDs were continued for months after clinical seizure cessation

References