Neonatal Seizures: Semioologies and Mechanisms

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Objectives, Neonatal Seizures

- Recognition/diagnosis
- Physiology
- Etiologies
- Treatment
- Research
- EEG
  - Bedside recording versus standard EEG
  - Basic EEG interpretation
A case.

• You are called from an outside hospital because they want to send you a term baby who was a failed home birth that they delivered via emergent C-section. Apgars were 8 and 9 and the baby went to Newborn Nursery. The child is now twelve hours old and mom felt the child having some jerking movements of his body when she was trying to breastfeed. The description of the jerking is really vague. The hospital wants to know if they should give the child Ativan or phenobarbital prior to transport, too.
Big Questions about Neonatal Seizures

- What do they look like?
- What is the best way to treat them?
- Do they affect cognitive outcomes?
- Does a diagnosis of neonatal seizures mean epilepsy?
- Why are neonates predisposed to have seizures?
Seizure Recognition in the Neonate

• Volpe’s four described semiologies
  – Subtle
  – Clonic
  – Tonic
  – Myoclonic
Seizure Recognition in the Neonate

• A large percentage of neonatal seizures (some say HALF) are clinically silent

• Behaviors that cause concern over seizure activity (so called “subtle” seizure activity)
  – APNEA
  – Eye deviation
  – Staring
  – Oral-buccal-lingual movements
  – Limb movements
  – Autonomic phenomena

• Varying reports of how often these behaviors are associated with electrographic seizure activity.
A Word about the Annoying Apnea

- Apneic seizures are less likely to be associated with bradycardia.
- Apneic spells are more likely to be a seizure in a term neonate than a preterm one.
Seizure Recognition, continued

• Clonic seizures are the semiology most likely to have an electrographic correlate.
• Tonic activity is not usually a seizure, unless accompanied by autonomic phenomena.
• Myoclonic activity, if generalized, is more likely to have an electrographic correlate.
Jitteriness or seizure?

- Jitteriness does not have ocular phenomena.
- Jitteriness is stimulus-sensitive.
- Jitteriness looks tremulous and seizures look jerky.
- Jitteriness is not accompanied by autonomic changes.
So what do I do if they’re doing something weird

• Observe and describe
  – Type of movement
  – Parts of body involved
  – Alterations in vitals
  – Number and duration of occurrences
  – Situation surrounding occurrence (i.e. “the baby arches their back whenever we try to get the IV”)

• While observing and describing: try to interrupt the behavior.
  – Rule of thumb: if you can’t interrupt it, it’s more likely to be a seizure.
And then...

• Call neurology and discuss whether to hook up to continuous EEG monitoring.
So there’s nothing on the EEG, so they aren’t seizures, right?

• We don’t actually know this for the neonate.
• In the human, real seizures CAN occur with a surface-negative EEG, which just looks at cortical activity.
  – Seizures can originate from deeper brain structures.
Why are neonates predisposed towards seizure?

• A seizure is excessive depolarization of neurons.
• Neurons in the newborn are predisposed towards excessive depolarization because of fundamental differences in their physiology with respect to:
  – Sensitivity to energy supply decreases
  – Excess of excitatory neurotransmitters
  – Deficiency of inhibitory neurotransmitters
  – Hypocalcemia or hypomagnesemia
Decreased energy supply in the neonatal neuron

• Conditions that do this
  – Hypoxic injury (HIE, stroke)
  – Hypoglycemia

• Decreased energy supply = less ATP

• Less ATP = Failure of the ATP-dependent Na/K pump
  – Normally keeps Na outside the cell and K inside
Excess of excitatory neurotransmitters

• Hypoxia and hypoglycemia in particular cause excess glutamate release
• Reduced ability to re-uptake glutamate
Deficiency of inhibitory neurotransmitters

• Decreased GABA
  – Reduced activity of glutamic acid decarboxylase (synthesizes GABA)
    • This enzyme is pyridoxine-dependent
  – Inhibitory synapses are not well-developed in the neonate
Deficiency of inhibitory neurotransmitters

• Excitatory synapses develop BEFORE inhibitory synapses
• More NMDA and AMPA receptors than adults
  – AMPA actually Ca-permeable at this stage
• GABA is actually EXCITATORY in the neonate
• Anticonvulsant projection network of the substantia nigra is not well-developed
Other causes of excessive depolarization

- Hypomagnesemia
- Hypocalcemia
- Both Ca and Mg reduce Na influx into the neuron
Did you just say GABA is excitatory?

- Normal GABA function in the adult:

  GABA activation

  →

  Cl influx

  →

  Hyperpolarization
GABA in the neonate

• Two GABA channels in the neonate
  – NKCC1: Cl influx
  – KCC2: Cl efflux

• Imbalance of these two channels in babies:
  – NKCC1 >> KCC2, leading to Cl influx
  – GABA activation occurs and Cl flows back down its new gradient and the overall effect is DEPOLARIZATION.
GABA in the neonate

- Phenobarbital is a GABA agonist, which is why it may not be optimum for neonatal seizures.
- Bumetanide inhibits NKCC1, blocking Cl uptake and making the neonatal neuron act more like a mature neuron.
Effects of Neonatal Seizures at the Molecular Level

• Seizures potentiate energy depletion by stimulating a lot of ATP-dependent ion pumping
• Increase in lactate production and acidity causes vasodilation
  – Increases cerebral blood flow
• Increase in BP during a seizure makes hemorrhage more likely (IVH)
• Sharp increase in glucose utilization creates a fall in brain glucose concentrations
Effects of Neonatal Seizures at the Molecular Level

• Glutamate excitotoxicity
  – Energy-dependent reuptake of Glu falls, creating accumulation of Glu
  – Glutamate receptors are richly expressed in the neonatal brain
  – To a pathologist, seizure-induced neuronal death is indistinguishable from glutamate-induced neuronal death
Effects of Neonatal Seizures at the Cellular Level

- Lack of energy substrates causes seizure-induced neuronal necrosis
- Single prolonged seizure $\rightarrow$ cell loss
- Brief recurrent seizures $\rightarrow$ altered neuronal development
  - Dendritic spine loss of CA3 cells of the hippocampus
  - Synaptic reorganization of mossy fibers
  - Increases in NMDA and AMPA receptors, creating potentially permanent predisposition towards excitation and epileptogenesis
Case Follow-up.

• The baby arrives and has had an episode en route of right arm and leg clonic jerking that was not extinguishable.

Seizure or not?
What do you do?

• Treat: phenobarbital 20 mg/kg iv load to start
  – Ativan okay for ongoing seizure or flurries of seizures while waiting for phenobarb from pharmacy
• Urgent HUS
• MRI if available
• Hook up to EEG monitoring
What Happened Next

• Child’s seizures did not stop with phenobarb load. Urgent HUS was normal.
  – EEG showed numerous seizures, only some of which had clinical correlates.
• Got another 10 mg/kg twice of phenobarb until seizure cessation clinically and on EEG.
• After a day of seizure freedom, the baby went to MRI.
Here is the MRI.

Take-Home Points: Recognition and Physiology

• Seizure recognition: observe and describe, ability to extinguish, context
• Neonates are physiologically predisposed towards seizure in many different ways.
• Given the excitatory nature of the neonatal GABA receptor, phenobarbital may not be the best choice for treatment of neonatal seizures. Results from trials of levetiracetam and bumetanide are anxiously awaited.
Neonatal Seizures: Etiologies

- The usual suspects
  - Hypoglycemia
  - Hypomagnesemia
  - Hypocalcemia
  - Hypoxic ischemic encephalopathy
  - Sepsis/central nervous system infection
  - Intracranial bleed
Neonatal Seizures: Etiologies

• Less common etiologies
  – Perinatal stroke/ sinovenous thrombosis
  – Cerebral dysgenesis
  – Genetic etiologies
    • Prader Willi/Angelman
    • Benign neonatal convulsions (“fifth day fits”)
  – Inborn errors of metabolism
“Rare as hen’s teeth” Etiologies

• Devivo’s disease
• Sulfite oxidase deficiency
  – Molybdenum cofactor deficiency
• Pyridoxine-dependent seizures
• Early epileptic encephalopathies
  – Ohtahara syndrome
  – “Channelopathies”
Etiologies with Unique Treatments

• HIE: cooling
• Vitamin-responsive encephalopathies
  – Pyridoxine
  – Pyridoxal-5-phosphate
  – Folinic acid
  – Molybdenum
• Devivo’s disease: ketogenic diet
Ohtahara Syndrome (EIEE)

- AKA: Early Infantile Epileptic Encephalopathy
- Burst suppression background on EEG
- Severe seizures: tonic spasms
- Usually due to structural defects
  - But can also be seen with encephaloclastic lesions (like HIE)
- Related to EME (Early Myoclonic Encephalopathy)
EME: Early Myoclonic Encephalopathy

- Severe neonatal seizures
  - Myoclonic, clonic, tonic spasms
- Burst-suppression background
- Usually due to metabolic etiology
- Half of cases are cryptogenic
Channelopathies

• Mutations in ion channels that regulate membrane potential or neurotransmission

• **SCN1A**

• Annals of Neurology Jan 2012: **KCNQ2**

• **KCNQ3**

• 4-5 others recently identified
Neonatal Seizures: Treatment

• First-line: phenobarbital
• Second-line: fosphenytoin or levetiracetam
• Third: fosphenytoin or levetiracetam
Neonatal Seizures: Treatment

• After these two or three:
  – Pyridoxine trial
  – Midazolam
  – Pentobarb
  – Other anticonvulsants
    • Topiramide
    • Carbamazepine
  – Hypothermia
  – Lidocaine
  – Paraldehyde
When is it status epilepticus?

• Definition varies

• Commonly accepted definitions
  – Seizures longer than 5 minutes
  – More than 50% of an hour spent seizing
Neonatal Seizures Research: Levetiracetam

- Pending
- Phase 2 RCT of LEV as first-line treatment for neonatal seizures
  - Dose escalation
  - Efficacy
Neonatal Seizures Research: Bumetanide

• Pilot study
• Phase I for PK and safety
• Standard phenobarbital plus either 0.1 mg/kg, 0.2 mg/kg, or 0.3 mg/kg of bumetanide as determined by the status of the dose escalation design.
  – Versus phb plus normal saline
Neonatal Seizures Research: Topiramate

• Italy: RCT of topiramate as adjunct for neuroprotection in cooled babies
• Primary endpoint is neurodevelopmental outcome
  – Not seizure cessation
• UM Center for Orphan Drug Research
  – Phase I PK and safety for IV TPM in adults
Neonatal Seizures Research: PROPHENO

- Multicenter RCT of neonates with seizures
- Randomized to discharge on phenobarbital versus no medications
- Cognitive outcomes followed
- Study recently terminated due to lack of enrollment
Persistent Neonatal Seizures

• Provoked seizures
  – Majority of seizures in the newborn
  – Most end with:
    • Treatment of underlying etiology
    • Anticonvulsants
    • “Burnout”

• Seizures persisting beyond multiple drugs or days:
  – Time to search for rare etiologies
Continuous Bedside EEG Recording

• Important in any neonate who is suspected of seizing
  – Half of neonatal seizures don’t show anything clinically
  – Neonates who are pharmacologically paralyzed or sedated
  – Encephalopathic neonates
Neonatal Seizures and Outcomes

• Neonatal seizures are bad for the brain and bad for developmental outcomes
  – We treat them aggressively
  – This is an opportunity to improve outcomes as much as possible by recognizing and treating seizures early
Basics of EEG

• Electroencephalography: the electrical activity of the brain
• Electrodes that record activity are glued on to the scalp
• Purpose:
  – 1. Quantify and localize subclinical seizures
  – 2. Evaluate background brain activity
The EEG setup

- Odd numbers are the left hemisphere
- Even numbers are the right hemisphere
- Cz is in the middle
- F=frontal
- O=occipital
- T=temporal
- P=parietal
- C=central
The EEG setup
The EEG setup
EEG recording
EEG recording: Seizures
EEG criteria for the neonatal seizure

• At least ten seconds in duration
• Evolution
  – Waveform
  – Field
  – Amplitude
  – Frequency
Pitfalls of EEG recording

• Background brain activity: random
• Seizures: rhythmic
• Other rhythmic things look like seizures if not otherwise noted
  – Patting, burping
  – Ventilator artifact
  – Chest PT
  – ECMO
Successful EEG recording

• OK to pat and burp and have chest PT
  – Just note it on the recording
  – Type and hit enter
  – OK to note after the fact!

• Note anything you are concerned about

• Anything looking like seizure on the EEG: notify the attending or NP
Are all my electrodes on?
Has the right type of EEG been ordered?

- Standard 1-hour EEG
- Bedside EEG recording
- Video EEG recording
How much monitoring do we need?

• 8-24 hours of seizure freedom
• Exception: hypothermia patients
  – Need to be continuously monitored
  – Until rewarming is complete
Duration of EEG Recording

• PICU literature: 8-24 hours after last seizure
• Still needs evaluation in the newborn
• Most institutions: 24 hours after last seizure in the NICU
Who should get continuous bedside EEG recording?

- Any baby suspected of seizure
- All hypothermia patients
- All ECMO patients
- All paralyzed patients
- Unexplained fluctuations in vital signs
Public Service Announcement for the NeuroNICU Consult Service

• We’re here for you!

• Stuff we see:
  – Seizures, HIE, stroke, extreme prematurity, high-grade IVH, other ICH, sinovenous thrombosis, multiple congenital anomalies, weakness, hypotonia, brachial plexus, contractures, etc.
Thank you