Seizure Recognition at the Bedside

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Neonatal Seizures

• Seizures are more common in the neonatal period than any other time in life (as high as 57.5/1000 in < 1500g and 2.8/1000 in 2500-3999) Volpe JJ. Neonatal Seizures. In: Neurology of the Newborn, 4th edition. 2000.

• With mod-severe HIE the incidence of seizures is > 50% Gluckman, Lancet 2005; Cool Cap Trial

• 11.5% of 183 neonates post heart surgery had unrecognized electrographic seizures Clancy, Epilepsia 2005
Importance of Accurately Recognizing and Appropriately Treating Seizures

- To evaluate possible underlying etiologies which may need specific treatments
- Uncontrolled/Untreated seizures may worsen long term outcome
- Antiepileptic medications in themselves can have side effects and/or long term detrimental effects

Neonatal Seizures Reliably Indicate Presence of CNS Dysfunction
Causes of Neonatal Seizures

Derived from Pressler, E-epilepsy

• **Hypoxic ischemic encephalopathy ~50%**
• Intracranial hemorrhage ~5-15% (increased in preterm infants)
• Meningitis/sepsis ~5-15%
• Cerebral Infarction ~5-15%
• Cerebral Malformations ~3-15%
• Metabolic
  – Hypoglycemia ~0.1-5%
  – Hypocalcemia, hypomagnesia ~ 4-22%
  – Inborn errors of metabolism, Pyridoxine dependency ~ 3-4%

Causes of Neonatal Seizures

Derived from Pressler, E-epilepsy

• Maternal Drug Withdrawal ~4%
• Idiopathic ~2%
• Benign neonatal seizures, neonatal epilepsy ~1%
Evaluation of Neonatal Seizures

- Septic evaluation including CSF
- CBC, Serum lytes (gluc, Ca, Mg, Na)
- Neuroimaging (Ultrasound, CT, &/or MRI)
- Tox/Drug screen
- Possible metabolic w/u (blood gas, lactate, pyruvate, ammonia, amino and organic acids)
- Possible trial of Pyridoxine
- Possible congenital (TORCH) infection w/u
- Possible serum bilirubin

Potential Brain Damage From Repeated Seizures

Neonatal Seizures may Adversely Affect the Developing Brain

- Evidence that neonatal seizures predispose infants to cognitive, behavioral, and epileptic complications in later life. *Levene, Arch Dis Child 2002*
- Seizures impair neurogenesis and derange neuronal structure, function and connectivity in animal models. *Holmes, Neuroreport 2002*
- Undetected and Untreated seizure activity increases the insult to the neonatal brain. *Wasterlain, Epilepsia 1997*
- Seizures add to hypoxic-ischemic insult in newborn animals. *Miller, Neurology 2002*

Given the Concern for Adverse Outcome of Infants with Untreated Seizures, Should We Just Treat Any Infant that is at Risk or Suspected of Having Seizures even Without Confirmation on EEG?
Certain Antiepileptic Drugs may also Adversely Affect the Developing Brain

- In immature rodent model, early exposure to phenytoin, phenobarbital, diazepam, clonazepam, and valproate caused apoptotic neurodegeneration Bittigau, Proc Natl Acad Sci 2002
- Phenytoin has been shown to induce cell death and faulty migration on granule and Purkinje cells in developing mouse cerebellum Ohmori, J Neurochem 1999
- Topiramate has not been shown to induce apoptotic neurodegeneration at therapeutic doses compared to phenobarbital, phenytoin, and valproate Glier, Exp Neurol 2004
- Concerns for prolonged use of phenobarbital increasing risk of behavior, learning, and memory problems

“Diagnosing seizures in the human newborn can be exceedingly difficult even for experienced observers” Clancy, Clin Perinatal 2006
Most Neonatal Seizures are Subtle or Subclinical (Not Clonic, Tonic or Myoclonic)

- Only approximately 20% of electrographic neonatal seizures provoke obvious clinical signs. Some infants have all subclinical seizures \textit{Mizrahi, Epilepsia 2001; Clancy, Epilepsia 2001}
- Preterm infants, infants with depressed brains, and infants on antiepileptic meds are more likely to have subclinical than clinical seizures

Some Clinical Seizures do not Correlate with EEG Seizure Activity

- Myoclonic seizures (especially focal and multifocal) and generalized tonic seizures are most often not associated with EEG seizure activity
Subtle Seizure Association with EEG Seizure Activity is Variable
Volpe, Neurology of the Newborn 4th ed 2000

- Tonic horizontal deviation of eyes + jerking have high EEG correlate in term infants
- Staring – high EEG correlate in preterm infants
- Autonomic phenomena (Apnea, Increased BP, Tachycardia) with EEG correlate is more commonly an isolated finding in Preterm and assoc with other symptoms in Term
- Theoretically some neonatal seizures may originate from brain stem or deep brain structures and variably transmit electrographically to the cortex

“Since seizures are difficult to determine, goal must be to eliminate electrographic neonatal seizures (ENS)” Clancy, Clin Perinatal 2006

Of course in order to accomplish this, we must first learn to recognize ENS at the bedside.....
Diagnosing Electrographic Neonatal Seizures (ENS)

• Standard EEG is gold standard
  – usually done for only 30 - 60 min
  – often not available emergently
  – often not done during suspected seizure activity
  – difficult to do in a continuous fashion
• Continuous aEEG can significantly enhance seizure detection

Comparison of Standard EEG and aEEG
(Prior to digitized “actual” or “raw” EEG visualization capability)

• 14/17 with Normal aEEG = Normal EEG
• 26/27 with Abnormal CFM = Abnormal EEG
  Naqueeib et al. - Pediatrics June 1999
• 15/15 = Agreement between background activity and seizure activity except very short (5-30s) seizures.
Comparison of Standard EEG and aEEG  
Toet et al. Pediatrics 2002  
(Prior to digitized “actual” or “raw” EEG visualization capability)

- 100% of severely abnormal aEEG’s (BS, continuous extremely low voltage, flat tracing) correlated with a severely abnormal EEG (excessive discontinuity, BS, low voltage undifferentiated, no activity) 100% PPV/Specificity, 80% NPV, 76% Sensitivity

- Agreement of background activity better with aEEG than EEG 0.92 vs 0.74

- aEEG reliable tool for monitoring normal and abnormal background patterns and ictal activity, but can miss certain focal, low amplitude and very short seizures

Sensitivity of aEEG for Seizure Detection  
Shellhaas et al Pediatrics 2007

- 851 neonatal seizures from 125 conventional EEG’s analyzed by 6 neonatologists
- Initial analysis done by 2 pediatric neurologists
- C3-C4 raw EEG recording converted to aEEG trace which was evaluated by 6 neonatologist
- 94% of EEG’s with seizures had seizures in C3-C4 location
- 78% of all individual seizures were seen in C3-C4 location
Location of Electrodes
(C3-C4 vs. P3-P4)

Sensitivity of aEEG for Seizure Detection
Shellhaas et al Pediatrics 2007

- "Original" EEG tracings "not" available to neonatologists. Only aEEG pattern could be evaluated
- Only 12%-38% of total of 851 seizures were detected
- Of 125 EEG's with seizures, seizures were detected in 22%-57%
- There were no false positives marked
- Correct seizure detection by aEEG improved with increased experience of neonatologist, seizure amplitude, seizure duration (av. 100 s) and frequency (av. 5.2/h)
We Must Look at “Actual” or “Raw” EEG Tracing along with aEEG pattern to Improve our Detection of Seizure Activity on aEEG

Definition of Electrographic Neonatal Seizure (ENS)

• A distinct electrographic event consisting of rhythmic activity with various morphologies, amplitudes, and frequencies with a definite beginning, middle, and end lasting at least 10 seconds in duration and minimum amplitude of 2 uV at beginning and end
Typical ENS

Clancy, Clin Perinat 2006; Shellhaas, Pediatrics 2007

- Begin focally (most commonly in central or temporal location) and evolve in amplitude and waveform morphology
- Commonly migrate from place of origin to adjacent areas and even to remote regions of opposite hemisphere (likely reason that most can be seen even with single channel EEG)
- Appearance/morphology varies among individuals
- Can occur with normal background voltage, but are most common with abnormal background voltage

Typical ENS


- Average duration is short (\(\leq 2\) min)
- Often rhythmic spikes at 2-3 Hz frequency but can be as slow as 0.5-1 Hz
- However can have much higher frequency (ie \(\geq 10-12\) Hz) especially with an alpha seizure discharge (usually sinusoidal pattern)
- Faster frequency discharges usually have lower voltages and slower frequency discharges higher voltages
- Frequency of discharges often correlates with frequency of clinical manifestations

aEEG Epileptic Seizure Activity Characteristics *Hellstrom-Westas, de Vries and Rosen, An Atlas of Amplitude-Integrated EEGs in the Newborn 2003*

- Transient rise in background activity
- Most commonly associated with rapid rise of both lower and upper margins of the tracing
- Status epilepticus or frequent seizures appear as a ‘saw-tooth’ pattern
Classical “Saw Tooth” Pattern of Frequent Seizures

aEEG Rapid Rise of Lower and Upper Margin of Tracing Associated with Seizure Activity
aEEG – Frequent Seizures with Abnormal Low Background Voltage

Low-Voltage, Rhythmic Sinusoidal Wave Activity with Depressed Background Voltage
Increase of aEEG Lower and Upper Margin Associated with Slow (~1 Hz) High-Voltage Sharp Waves ("Raw" EEG at 15 mm/sec)

Increase of aEEG Lower and Upper Margin Associated with Slow (~0.5 Hz) Moderately High-Voltage Slow Waves ("Raw" EEG at 30 mm/sec compared to 15 mm/sec)
High Frequency/Low Voltage Rhythmic Activity in Premature Infant Associated with Increased BP

Very Short and Continuous Seizures May be Difficult to Detect on aEEG without Evaluating “Actual” or “Raw” EEG Component

- Continuous seizure activity may not show classical aEEG background and instead may show a persistently elevated background
- Seizures < 20-30 seconds difficult to detect on aEEG alone
Example of Continuous Seizures on aEEG

Short ~ 30 Second Seizure

Examples of Artifact on aEEG
Myoclonic Artifact With Forehead Hydrogel Electrode Placement

High Frequency Ventilation Artifact (Rate 8 Hz)
High Frequency Ventilation (Rate 10 Hz) Artifact With aEEG Abrupt Change with Turning Head

Conventional Ventilation Artifact with Ventilator Rate of 15
EKG Artifact

EKG Artifact Causing False Elevation of aEEG Background
aEEG and “Raw” EEG Artifact from Displacement of Electrodes

Tips on Decreasing and Interpreting Artifact

- Use needle electrodes in biparietal location (Needle electrodes should not be used in forehead location)
- Avoid forehead application if possible as it will pick up more eye and myoclonic movement
- Free electrode wires from equipment which may cause movement artifact and secure electrode wires well to head
Tips on Decreasing and Interpreting Artifact

- Have nurses mark suspected seizure activity as well as cares (diaper change, feeding, moving, holding) procedures, and medication administration (phenobarbital, phenytoin, benzodiazepams, narcotics)

- Consider administering a muscle paralyzing agent such as succinyl choline, pancuronium, or vecuronium if unable to distinguish movement artifact (ie. gasping or myoclonus) from seizure activity and patient is being mechanically ventilated