Neonatal Seizures – Part I

Krisa Van Meurs, M.D.
Rosemarie Hess Professor of Neonatal and Developmental Medicine
Stanford University School of Medicine
Medical Director, Neuro NICU
Lucile Packard Children’s Hospital

5 Minute Friday
February 3, 2017
Significance of Neonatal seizures

• Neonatal seizures may be the first and only clinical sign of a central nervous system disorder in a newborn.

• Seizures may indicate the presence of a treatable condition prompting important evaluation and treatment.

• Seizures may contribute to further brain injury.
Definition of neonatal seizures

**Definition:** Paroxysmal behavior caused by hypersynchronous discharge of a group of neurons.

**Classification:**

- **Clinical only seizure:** Sudden paroxysm of abnormal clinical changes with no correlation with simultaneous EEG seizure

- **EEG only seizure (sub-clinical seizure):** Definite EEG seizure not accompanied by any visible clinical signs

- **Electro-clinical seizure:** Definite clinical seizure signs coupled with EEG seizure
Percentage time electrographic seizures had clinical signs recognized by clinicians

**Uncoupling or electro-clinical dissociation**

**Definition:** Persistence of electrographic seizures despite suppression of ≥50% clinical seizures

**Methods:** 50 newborns with EEG and clinical seizures treated with either phenobarbital or phenytoin

**Results:**
- 24 had no EEG or clinical seizures
- 26 had persistent seizures: 5 EEG only
  - 10 ≥ 50% suppression clinical seizures
  - 11 < 50% suppression clinical seizures

**Conclusion:** 58% newborns had “uncoupling” with only or predominantly EEG seizures following treatment with anticonvulsants

Status epilepticus

- The traditional definition of status epilepticus in adults and children is a continuous seizure or multiple seizures without a return to normal neurologic baseline, lasting at least 30 minutes.

- This definition is less useful in newborns as seizures are more subtle and neurologic baseline is harder to identify.

- Proposed definition in neonates is seizures present in over 50% of recorded epoch. Pisani F, et al. *Neuropediatrics* (2016)

- Status epilepticus in newborns is associated with worse outcomes than seizures of shorter duration.
The American Clinical Neurophysiology Society’s Guideline on Continuous Electroencephalography Monitoring in Neonates

Renée A. Shellhaas,* Taeun Chang,† Tammy Tsuchida,‡ Mark S. Scher,‡ James J. Riviello,§ Nicholas S. Abend,|| Sylvie Nguyen,¶ Courtney J. Wusthoff,# and Robert R. Clancy||

Clinical guidelines for cEEG monitoring
cEEG recommendations by American Clinical Neurophysiology Society (ACNS)

1. Neonates at high risk for seizures should be monitored for 24 hours to screen for seizures. If seizures are detected, monitoring should continue until seizure-free for at least 24 hours.

2. Review by neurophysiologist after first 1 hour then twice daily or more often as clinically indicated with daily written reports.

3. Bedside observer is needed to document clinical events (e.g. suspected seizures, drug administration, chest PT or feeding)

4. Concurrent cEEG with digital trend display of aEEG tracing to be utilized by bedside providers trained in aEEG interpretation.

Etiologies of neonatal seizures

- Hypoxic ischemic encephalopathy (HIE)
- Intracranial hemorrhage (intraventricular, intracerebral, subdural, subarachnoid)
- Central nervous system infection (meningitis, encephalitis, intrauterine)
- Cerebral infarction (stroke)
- Metabolic causes (hypoglycemia, hypocalcemia, hypomagnesemia)
- Chromosomal abnormalities
- Inborn errors of metabolism
- Brain malformations
- Neurodegenerative disorders
- Benign neonatal convulsions or benign familial neonatal convulsions
- Drug withdrawal or intoxication
Phenobarbital versus Phenytoin for neonatal seizures

**Purpose:** Determine most efficacious treatment for seizures

**Methods:** 59 newborns with EEG confirmed seizures

**Results:**
- Phenobarbital: 43% seizures controlled, \( p=1.0 \)
- Phenytoin: 45% seizures controlled
- Phenobarbital + Phenytoin: 57%, \( p=0.67 \)
- Phenytoin + Phenobarbital: 62%

Seizure severity was a stronger predictor success than the drug used

**Conclusions:** Both drugs are equally and incompletely effective as anticonvulsants in neonates

First line therapy for seizures

Phenobarbital loading dose 20-30 mg/kg IV

Seizures resolve?

Yes

- Begin maintenance phenobarbital 12 hours after loading (4-6 mg/kg/d in 2 divided doses).
- Continue EEG monitoring until patient is seizure-free for 24 hours

No

- Repeat 10-20 mg/kg IV phenobarbital boluses to bring phenobarbital level up to ~50 micrograms/mL or maximum of 50 mg/kg in 24 hours
- Begin or continue EEG monitoring
Neonatal Seizure Registry data

**Diagnoses:** HIE 38%, stroke 18%, ICH 12%, Genetic 6%, CNS Infection 4%, CNS Malformation 4%, Transient metabolic 4%, Inborn error of metabolism 3%, Benign neonatal epilepsy 3%, unknown 9%

**Mortality:** 17%

**Seizure burden:** 59% ≥7 seizures, 16% status epilepticus, 52% ≥2 medications

**Seizure management:**

- **Initial loading medication:**
  - Phenobarbital 89%, Levetiracetam 5%, Fosphenytoin 1%, no loading 4%

- **Seizure treatment during hospitalization:**
  - Phenobarbital 92%, Fosphenytoin 28%, Intermittent benzodiazepine 20%, benzodiazepine infusion 7%, Topiramate 4%, carbamazepine 2%, vitamins 8%
Efficacy of Levetiracetam in neonatal seizures

**Primary outcome:** To determine the efficacy of IV Levetiracetam 40-60 mg/kg in controlling seizures compared to phenobarbital 20-40 mg/kg when given as first line therapy.

**Secondary outcomes:**
- Pharmacokinetic and safety data
- Efficacy of higher doses in reducing seizure burden
- Feasibility of remote monitoring of cEEG and accuracy of a seizure detection algorithm

**Target enrollment:** 100

**PI:** Richard Haas, MD University of California San Diego

NCT01720667