Neonatal Seizures: Diagnosis and Management

Dr Prashanth Murthy
Outline

• What makes the newborn brain epileptogenic?

• Examples of types of neonatal seizures

• Diagnostic tools:
  • aEEG
  • EEG
  • Video EEG

• Treatment

• Seizures and Long term outcome
Case Exemplar

• Term infant, difficult delivery due to shoulder dystocia

• Emergency C/S, baby flat with poor APGARS

• Resuscitation: PPV, intubation

• Clinically baby floppy and encephalopathic

• Hypothermia initiated

• Desaturations with bradycardia
Clinical Course

• Tonic seizure correlated with EEG changes
• Loaded with phenobarbitone X 2
• Continued to have electrographic seizures
• Phenytoin added for ongoing seizure activity
• Poor seizure control, multiple seizures
• 3rd medication added (levetiracetam)
• Seizures subside by 48 hours of age
Why is Infant Brain Epileptogenic?
Newborn Brain is Epileptogenic

Causes:

• GABA Signaling

• Glutamate Signaling

• Channel Expression

• Network maturation

Anna-Maria Katsarou et al, Epileptogenesis in neonatal brain, Seminars in Fetal and Neonatal Medicine, Volume 23, Issue 3, 2018
What Causes Neonatal Seizures?

- Hypoxic ischemic encephalopathy (38%)
- Ischemic stroke (18%)
- Intracranial hemorrhage (12%)

Other Causes:
- Acute metabolic disorders
  - Hypocalcemia
  - Hypoglycemia
  - Hypomagnesemia
  - Hyponatremia or hypernatremia
- Sepsis
- Brain Malformations
- Inborn error of metabolism
- Genetic Syndromes
- Miscellaneous

Types of Seizures

4 main types

1. Subtle (~50%)

2. Clonic (20-30%)

3. Myoclonic (15-20%)

4. Tonic (~5%)
Subtle Seizures

• ‘Not obvious’
  • Orofacial manifestations
  • Limb movements
  • Autonomic
• Commoner in preterm infants
• Inconsistent EEG correlation
• EEG changes most likely with ocular manifestations
• ‘Subtle’ seizures may cause significant neurological injury
Clonic Seizures

• Usually one limb / one side

• Rhythmic Jerking (frequency 1-4/second)

• Characteristic EEG change (sharp slow waves)

• Seizures may migrate from one limb to another

• Associated with focal lesions

• Infants often conscious
Tonic Seizures

• Least common seizure type

• Can be either focal or generalized (more common)

• Persistent posturing of limb

• Often associated with eye deviation

• Poor EEG correlation
Myoclonic Seizures

- Sudden and brief jerky movements of flexor muscles
- Localized or generalized
- Generalized myoclonus associated with EEG changes
- Preterm infants with major cerebral pathology
- Midazolam weaning
- Distinguished from clonic seizures by lack of rhythmicity and rapidity
- Myoclonic jerks also lack the slow return phase of clonic movements
Myoclonic Jerks
Diagnostic Approach

• Does my patient have seizure?
  • Clinical diagnosis
  • EEG diagnosis

• What type of seizure does my patient have?
  • Clinical
  • EEG
Clinical Clues

• Antenatal and birth history
• Age of onset
• Family history
• A detailed clinical description of movement
• A thorough general physical and neurological examination
Diagnostic Tools - aEEG

• aEEG is a filtered and compressed EEG trend

• Prognostically significant data regarding background
  • Bedside tool
  • Several hours of data displayed on a markedly compressed time scale
  • Studied in numerous clinical scenarios (HIE, sepsis and prematurity)
  • Simple criteria (al Naqeeb and L. Hellström-Westas et al)

Al Naqeeb

Classification based on bands of activity 10 μV and 5 μV

Pattern recognition as well as voltage criteria

- Continuous
- Discontinuous
- Burst Suppression with reduced bursts
- Continuous Low Voltage
- Burst Suppression with increased bursts
- Isoelectric
aEEG

- Simple and valuable bedside tool
- Excellent for measuring background brain activity
- aEEG as a seizure detection tool is less than desirable
- Shorter seizures often missed with only around 30% of single seizures detected
- Long seizures and status often detected
- Seizure detection is improved with ‘seizure detection’ software
- Detection improved with more electrodes
EEG

• Conventional EEG - Gold standard for the diagnosis and quantification of NS

• **Seizure**: Repetitive, rhythmic, stereotypic activity lasting at least 10 seconds (Both amplitude and morphology is involved)

Indications:
  1. Evaluation of abnormal paroxysmal events
  2. Surveillance for subclinical seizures
  3. Assessment of EEG background activity

• Mean duration of electrographic seizures is ~2-3 mins, 97% of all seizures last < 9 mins.

• 0.4% last longer than 30 mins

*Clancy R.R., Ledigo A.: The exact ictal and interictal duration of electroencephalographic neonatal seizures. Epilepsia. 28:537-541 1987*
Video EEG

• Combining a time stamped video clip with EEG

• Become the ‘Gold Standard’ for several clinical questions

• Indications:
  • All infants with hypoxia undergoing cooling
  • Infants with encephalopathy
  • Any suspected seizure, seizure like activity
  • Infants with seizures undergoing treatment
**Duration for EEG Recording**

- Depends on the indication for testing

<table>
<thead>
<tr>
<th>Indication</th>
<th>Suggested Duration</th>
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<tbody>
<tr>
<td>Evaluate for electrographic seizures</td>
<td>24 hours</td>
</tr>
<tr>
<td>Monitoring after confirmation of electrographic seizures</td>
<td>Until neonate has been seizure free for 24 hours</td>
</tr>
<tr>
<td>Differential diagnosis of paroxysmal events</td>
<td>Until at least 3-4 events have been recorded</td>
</tr>
<tr>
<td>Characterization of EEG background</td>
<td>Serial routine length (60 min)</td>
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</table>

Diagnostic Tools - Additional Investigations

Investigations tailored to individual scenarios

• Full sepsis work up

• Glucose, electrolytes, Liver function tests

• Metabolic work up (lactate, pyruvate, ammonia, plasma amino acids, urine organic acids, and sometimes cerebrospinal fluid for neurotransmitters, lactate, and amino acids)

• Genetic testing (microarray or specific gene testing)

• Cranial USS, USS of abdomen

• ECHO
Diagnostic Tools - Neuroimaging

**Imaging modality of choice: MRI**

- A combination of MRI sequences (T1, T2 and diffusion weighting) will allow detection of most intra- and extra-axial bleeds
- MR angiography + neck vessels included when stroke is suspected
- Timing of MRI scan dependent on clinical presentation
Antiepileptics
Treatment Regimens

- Initiating therapy with phenobarbital
- Adding either a benzodiazepine or phenytoin or lidocaine as a second-line agent


- Starting with phenobarbital
- Levetiracetam, phenytoin or lidocaine - 2nd line
- Benzodiazepine – 3rd agent


- Increase in Levetiracetam use
- A survey of clinicians in the USA found that a majority (73 %) would use levetiracetam and/ or topiramate

Levetiracetam

- Broad spectrum anti-seizure medication
- Acts on synaptic vesicle glycoprotein 2A (SV2A), a protein believed to be involved in the release of neurotransmitters

Favorable features include:
- Linear pharmacokinetics
- Rapid absorption (within 30 min)
- Non-hepatic elimination
- Lack of protein binding (< 10%)
- No drug-drug interaction with other medications
- Relatively short half-life compared to PB
- LEV does not increase apoptosis in a developing rodent brain or interfere with neuroprotective mechanisms.

Head to Head Comparison with Phenobarbitone

Comparative Effectiveness of Levetiracetam vs Phenobarbital for Infantile Epilepsy

- Prospective, multicenter, observational cohort study of children with epilepsy that began in the first 3 years
- Use of levetiracetam or phenobarbital as initial monotherapy

Results:

- Infants treated with levetiracetam were free from monotherapy failure more often (47 [40.2%] vs 6 [15.8%]; \( P = .01 \))

- If 100 infants received Levetiracetam only instead of phenobarbitone only, 44 would be free from monotherapy failure instead of 16

Antiepileptic use in our Institution

Seizure

- Phenobarbital
  - 20 mg/kg load up to 40 mg/kg total
  - or to level 160-200

- Fosphenytoin
  - 15-20 mg/kg

- Levetiracetam

- Topiramate
  - Or
  - Lorazepam
    - 0.1 mg/kg up to 2 times
    - Then
    - Midazolam infusion 60-600 mcg/kg/hr
Seizure and Short Term Effects

• Seizures can contribute to depletion of energy reserves by increase in brain metabolism

• Disruption of blood brain barrier

• Derangement of cerebral autoregulation

• Work with neonatal rats has suggested that glucose may have a protective effect in electroshock-induced seizures

Seizures - Long Term Effects

• Prospective population based study of 5 years from Newfoundland (1990-95)

• 90 cases with seizures

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<thead>
<tr>
<th></th>
<th>Term</th>
<th>Preterm</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>45%</td>
<td>12%</td>
</tr>
<tr>
<td>Deaths</td>
<td>16%</td>
<td>42%</td>
</tr>
<tr>
<td>Impairments</td>
<td>39%</td>
<td>46%</td>
</tr>
</tbody>
</table>

• Prognosis better for term infants
• 27% of survivors developed epilepsy
• 25% had cerebral palsy
• 20% had mental retardation

Gabriel M. Ronen et al Neurology Nov 2007, 69 (19) 1816-1822
Seizures - Long Term Effects


- Retrospective study (10 years)
- Single center
- 168 neonatal seizures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Normal without epilepsy</td>
<td>71%</td>
</tr>
<tr>
<td>Neurological Abnormality</td>
<td>19%</td>
</tr>
<tr>
<td>Intellectual Disability</td>
<td>17.2%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>7.4%</td>
</tr>
<tr>
<td>Death</td>
<td>4.2%</td>
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- Unfavorable outcome associated with abnormal EEG background, resistant seizures and low APGAR scores
Seizures - Long Term Effects

• Seizures associated with significant long term sequelae

• Prolonged seizures and status in HIE – adverse neurodevelopmental outcome
  • Low birthweight
  • Abnormal EEG
  • Abnormal MRI

• Estimates of epilepsy vary widely, 17.9% in a review of over 44 studies
  Pisani, Francesco et al. Epilepsy after neonatal seizures: Literature review European Journal of Paediatric Neurology, Volume 19, Issue 1, 6 - 14
Conclusion

• Common problem in the neonatal period
• Significant developments in detection
• Several treatment guidelines
• Research in AEDs lacking
• Leviteracitam gaining popularity
• Optimal duration of drug administration for neonatal seizures not known
Identify this Movement
Please Vote

a) Tonic seizure
b) Clonic seizure
c) Myoclonic jerks
d) Subtle seizures
e) None of the above
Please Vote

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b) Clonic seizure

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Please Vote

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Identify Seizure
Please Vote

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Please Vote

a) Tonic seizure
b) Clonic seizure
c) Myoclonic jerks
d) Subtle seizures
e) None of the above
Is there a seizure?
Please Vote

a) Yes

b) No
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