Neonatal seizure - diagnosis and treatment

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Neonatal seizures

- Incidence of seizures:
  - 0.5-3 per 1,000 term live births
  - 10-130 per 1,000 preterm live births
- Seizure classification
  - ILAE (NS currently not included)
  - Volpe (1989, 2008)
  - Mizrahi (1998)
- Nearly all acute seizures
  - birth asphyxia (HIE)
  - vascular
  - infections
  - Epilepsy syndromes <5%


Neonatal seizure - classification

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>EEG</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtle</td>
<td>+/-</td>
<td>50%</td>
</tr>
<tr>
<td>Clonic</td>
<td>+++</td>
<td>25%</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>+ if generalised</td>
<td>20%</td>
</tr>
<tr>
<td>Tonic</td>
<td>- if generalised</td>
<td>5%</td>
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</tbody>
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Volpe 1989/2008

Hypoxic Ischaemic Encephalopathy (HIE)

- 2-4/1000 full term births
- APGAR < 3/5, cord pH < 7.0
- Grading (Sarnat & Sarnat):
  - I - irritability, no seizures, poor sucking
  - II - lethargy, ± seizures, no sucking
  - III - comatose, prolonged seizures, no spontaneous respiration
- EEG background prognostic indicator

Epilepsy syndromes with seizure onset in neonatal period

- Benign idiopathic neonatal convulsions (5th day fits)
- Benign familial neonatal convulsions
- Early-infantile epileptic encephalopathy with burst-suppression pattern (Ohtahara syndrome)
- Early myoclonic encephalopathy
Benign idiopathic neonatal convulsions (5\textsuperscript{th} day fits)

- **Aetiology:** unknown, low CSF zinc / B6 / B12
- **Onset:** day 4-6 in 90%
- **Seizures:** clonic ± apnoeic, resolves within days
- **EEG:** th\(\acute{e}\)ta pointu alternant or normal
- **Therapy:** should be treated for up to 10 days
- **Outcome:** good

Benign familial neonatal convulsions

- **Onset:** day 2-3
- **Aetiology:** AD, KCNQ2-20q, KCNQ3-8q. (BFNIS: SCN2A-2q)
- **Seizures:** Clonic, apnoeic, resolve within weeks
- **EEG:** Normal
- **Therapy:** Controversial, might not be necessary
- **Outcome:** Sec. epilepsy ↑

Early myoclonic encephalopathy

- **Onset:** 1st month
- **Aetiology:** Metabolic
- **Seizures:** Myoclonias predominate
- **EEG:** Burst-suppression pattern
- **Therapy:** Resistant to treatment
- **Outcome:** Poor prognosis
- **Case:** Consanguine patients, GA 33 weeks, seizures, aromatic-L-aminoacid decarboxylase deficiency

Early-infantile epileptic encephalopathy with burst-suppression pattern (Ohtahara syndrome)

- **Onset:** First 3 mon.
- **Aetiology:** cerebral malformations
- **Seizures:** tonic, partial seizures
- **EEG:** Burst-suppression pattern
- **Therapy:** Resistant to treatment
- **Outcome:** Poor, infantile spasms

Metabolic errors of metabolism

- Pyridoxine dependent seizure
- Pyridoxal-5-phosphate dependent seizure
- Folinic acid responsive seizures
- Glucose transporter type 1 syndrome
- Propionic aciduria
- Glycine encephalopathy (neonatal non-ketotic hyperglycinaemia)

Seizures - a clinical diagnosis?

- 20 video clips of 11 seizures and 9 other events
- Evaluated by 137 health professionals (US, Ire, UK)
  - 91 doctors (consultants, fellows, residents)
  - 46 NICU nurses / midwives
- Asked to identify seizures vs non-seizures
- Correctly identified events: 10/20 in average
  - Conic seizures most frequently identified
  - Others poorly
- Poor agreement with correct diagnosis (0.09/-0.02)
- Poor inter-observer agreement (0.21/0.29)

Malone et al 2008
Clinical seizure detection

- 51 high risk babies with cEEG
- 12 babies with electro-clinical clinical or electrical seizures
- Clinical diagnosis of seizures
  - Under diagnosis in ~90%
  - Over diagnosis in ~70%
- Clinical seizures activity in 20% of total EEG seizure burden

Murray et al 2009

Investigations

- Glucose, urea & electrolytes, blood gas
- FBC & differential
- Lumbar puncture, blood and urine cultures
- Cranial ultrasound scan
- EEG, CFM/CFAM for monitoring
- MRI, CT
- Screen for maternal drugs abuse
- Virology and congenital infection (TORCH)
- Metabolic screen
- Trial of pyridoxine, pyridoxal 5 phosphate, folic acid

Neonatal EEG: Gold standard

Poor concordance between clinical and electrical evidence
⇒ necessity for EEG diagnosis


- ECG
- Respiration
- EMG
- EOG
- Video
- Full / reduced montage
- Duration: 40-60min (incl wakefulness & sleep)

De Weerd et al., 1999

EEG features of neonatal seizures

- Any rhythmic activity is suspicious
- Sudden and distinct beginning & end
- Focal origin with spread
- Evolution of amplitude & morphology
- Minimum duration ≥10 sec
- Often ill sustained
- Status: >50% seizure activity in 30 min EEG

Brief Interictal Rhythmic Discharges (BIRDs)

Discharges <10 s of uncertain significance?

- Occur in premature and sick neonates
- Associated with seizures in same/other EEG
- Associated with poor neuro-developmental outcome

Shewmon, 1990; Oliveira et al. 2000

Diagnosing neonatal seizures

- Cot-side cerebral function monitor (CFM, aEEG)
- 1-2 channels of amplitude integrated EEG
- Disadvantage: susceptible to false positive and negative errors
Treatment - current practice

- **First line**
  - Phenobarbital

- **Second line**
  - Phenytoin (US)
  - Clonazepam (UK)
  - Midazolam (UK)
  - Diazepam
  - Lignocaine (S, NL)
  - Sodium valproate
  - Lorazepam


Evidence base for the treatment of Neonatal Seizures
(Cochrane Report Booth and Evans 2004)

- **Primary objective:**
  - Not only seizure frequency, but reduced mortality / long-term disability
- **Only 2 adequate trials (RCT with EEG monitoring)**
- **Conclusion:**
  - Little evidence from randomised trials to support the use of any AED currently in use in the neonatal period

AED and electroclinical dissociation

Boylan et al, 2003

Age dependent mechanisms of seizures in the immature brain

- Enhanced excitatory neurotransmission
  - GABA excitatory
  - GluR-mediated excitation
- Neuropeptides increase hyperexcitability
- Ion channel configuration favours depolarization
- Reduced inhibitory neurotransmission

Ben-Ari Y & Holmes GL Lancet Neurol, 2006; Jensen F 2010

New approaches

- **Topiramate**
  - Neuroprotective properties,
  - Unfavourable safety profile in children.
- **Lignocaine**
  - Local anaesthetic/antiarrhythmic drug.
  - Narrow therapeutic window, PK prolonged with cooling.
- **Levetiracetam**
  - Safety and PK/PD not studied in newborns.
  - Case reports and retrospective studies without EEG.
- **Bumetanide**
  - Loop diuretic, good safety profile as diuretic.
  - Feasibility studies ongoing: Boston study (US), NEMO (EU)

Conclusion – Neonatal Seizures

- NS are usually acute requiring immediate diagnosis and treatment
- Clinical diagnosis not better than tossing a coin
- EEG monitoring is a necessity for diagnosis and treatment monitoring
- Current AED treatment is inadequate
- New drug development requires EEG monitoring
- Multidisciplinary approach benefits babies