Incidence of neonatal seizures in a NICU population

The incidence of seizures is higher in the neonatal period than in any other age group.

<table>
<thead>
<tr>
<th>Standard EEG</th>
<th>2.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheth RD et al; Ped Neurol 1999</td>
<td></td>
</tr>
<tr>
<td>Standard EEG + aEEG</td>
<td>4.5%</td>
</tr>
<tr>
<td>Hellström-Westas L et al; Arch Dis Child 1995</td>
<td></td>
</tr>
<tr>
<td>Continuous EEG in high risk population</td>
<td>20%</td>
</tr>
<tr>
<td>Connell J et al; Arch Dis Child; 1989</td>
<td></td>
</tr>
<tr>
<td>Helmers SL et al; Electroenceph Clin Neurophysiol 1997 (cardiac)</td>
<td></td>
</tr>
</tbody>
</table>

Estimated frequency of 80-120 cases per 100,000 neonates per year has been suggested.

The Current Etiologic Profile and Neurodevelopmental Outcome of Seizures in Term Newborn Infants

Tekgul et al; Pediatrics 2006; 117(4):1270-80

![Diagram](image)

The relationship between the onset of electrographic seizure activity after birth and the time of cerebral injury in utero.


Babies with prelabour insults had their first seizures before 12 hours of age, whereas those whose insult was peripartum had seizure onset at 18-20 hours of age.

When?

- Most seizures will start within the first day after birth
- Very early onset may indicate antenatal onset of an adverse event
- Infants with - perinatal stroke - metabolic disorders - CNS infection will develop seizures later during the first week

Predictive Value of Clinical and EEG Features in the Diagnosis of Stroke and Hypoxic Ischemic Encephalopathy in Neonates With Seizures

Rafay MF et al; Stroke 2009

| Table 1. Comparison of Clinical Characteristics of Neonates With Stroke and HIE |
|-----------------|-------------|----------|---------|--------|
|                  | Stroke (n=21) | HIE (n=20) | OR (95% CI) | P value |
| Neuronal abnormality* | 13 (62) | 6 (30) | 2.81 (1.09-6.93) | 0.03 |
| Seizure | 9 (43) | 8 (40) | 1.05 (0.41-2.73) | 0.93 |
| Time to onset of first seizure (hr) | 12 (6-34) | 9 (4-32) | 2.01 (0.51-8.10) | 0.35 |
| Neonatal death | 7 (33) | 10 (50) | 1.05 (0.41-2.73) | 0.93 |

* Denotes *p* value; CI, confidence interval; OR, odds ratio; *p* values were calculated using the chi-square test; *p* values less than 0.05 were considered significant.

![Table](image)
What we do know

- Success of the most commonly used anti-epileptic drugs is moderate to poor
- 50-70% of the seizures are subclinical

Do not know

- Do we need to treat clinical as well as subclinical seizures?
- Is treatment with AED harmful for the developing brain?

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Subclinical Seizures

- About 60% of all seizures in newborn infants are subclinical
- "Uncoupling" is especially common following initiation of treatment of clinical seizures (Boylan, Arch Dis Child 2002; Scher, Pediatr Neurol 2004)

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Uncoupling of EEG-clinical neonatal seizures after AED; (Scher MS; Pediatr Neurol; 2003;28:277)

- 59 infants with Neonatal seizures
- n=9 Electrographic only
- n=50 Clinical and electrographic
- n=24 No seizures after AED
- n=26 Seizures continued 15/26 uncoupling

---

Electrophysiological Seizures

- Murray et al; Arch Dis Child, FFN 2007
- n=9 children
- 526 seizures

- Staff detected
  - n=48/526 of all seizures (9%)
  - and 48/179 of all clinical seizures (27%)

- Staff overdiagnosed
  - Suspected but not EEG confirmed
  - n= 129/177 (73%)

---

Poor electrographic response to phenobarbitone; (Boylan GB et al; Arch Dis Child 2002; 86: F165-70)

Electroclinical

Case 4

Electrographic

Case 8

---

Full-term, IVH+flaring
Very resistant to AED

---

Uncoupling of EEG-clinical neonatal seizures after AED; (Scher MS; Pediatr Neurol; 2003;28:277)
Neurodevelopmental outcome in term infants with status epilepticus detected with aEEG.
Van Rooij L et al; Pediatrics 2007; 120(2):e354-63

Subclinical SE from 1.00-9.00

Phenob

Associated background pattern best predictor of outcome

Neurodevelopmental outcome in full term infants with Status Epilepticus detected with aEEG
Neonatal status epilepticus vs recurrent neonatal seizures: Clinical findings and outcome
Pisani F et al; Neurology 2007;69;2177-2185

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight  ≤ 1,500-2,499 g</td>
<td>27.074</td>
<td>1.921-381.846</td>
<td>0.015</td>
</tr>
<tr>
<td>500-999 g</td>
<td>266.290</td>
<td>4.341-16,932.732</td>
<td>0.006</td>
</tr>
<tr>
<td>Cerebral ultrasound findings (IVH degree III or IV, PVL, intraparenchymal hemorrhage, brain reorganization)</td>
<td>200.117</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>Presence of status epilepticus</td>
<td>492.506</td>
<td>6.179-39,237.607</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Note: IVH = intraventricular hemorrhage, OR = odds ratio, PVL = periventricular leukomalacia.

Comparison between phenobarbital and phenytoin; Painter et al; NEJM 1999

- Randomised study for phenobarbital or phenytoin. When lack of seizure control, the second drug was added.
- 43% seizure control for phenobarbital and 45% for phenytoin treatment
- combined treatment resulted in seizure control in 57% when phenobarbital was the first drug and 62% when phenytoin was the first drug.

Seventy-three percent (40/55) recommended treatment of neonatal seizures with one or both of levetiracetam and topiramate; 47% (26/55) recommended levetiracetam; and 55% (30/55) recommended topiramate.

Neonatal seizures can be due to numerous causes, including hypoxic-ischemic encephalopathy, congenital infections, and structural anomalies. The management of neonatal seizures is critical to prevent neurodevelopmental sequelae. The choice of antiepileptic medication is based on the clinical presentation and the underlying cause of the seizures. Phenobarbital and phenytoin are commonly used first-line treatments. However, if initial treatment fails, a second antiepileptic medication may be added. Studies have shown that the combination of phenobarbital and phenytoin can improve seizure control compared to monotherapy. It is important to monitor for adverse effects and adjust the treatment plan as needed. Further research is needed to identify the most effective and safe treatment strategies for neonatal seizures.
Prolonged seizures exacerbate perinatal HI brain damage
Wirrell EC et al Ped Res 2001

- Convulsions were induced with Kainic acid with or without previous Hypoxia-Ischemia
- Convulsions per se did not lead to neuronal damage to the immature brain
- A strong increase in damage to the neonatal brain associated with neonatal seizures was noted when the rat brain had previously been exposed to HI (hippocampus)

Mean damage score for rat pups receiving 30 min HI (group V) or 30 min HI+KA (group VI)

However
Anti-epileptic drugs and apoptotic neurodegeneration in the developing brain.
Phenobarbital, phenytoin, diazepam and clonazepam cause apoptotic neurodegeneration in the developing rat brain at plasma concentrations relevant for seizure controls in humans

Expose to an enriched environment in weanling rats significantly improves visual–spatial learning.
Even following SE, an enriched environment enhances cognitive function.

Beneficial effects of enriched environment following status epilepticus in immature rats.

Early-life experience alters response of developing brain to seizures.

Cerebral metabolic effects of neonatal seizures measured with in vivo 31P NMR spectroscopy.
Younkin DP et al; Ann Neurol 1986; 20:513
Electrographic seizures in neonates correlate with poor outcome
McBride et al; Neurology, 2000; 55:506

- 68 infants studied with EEG, most >34 wks; 40 developed seizures
- 43% of the children with seizures spent 38 minutes up to 32 hours in electrographic status
- seizures were correlated with microcephaly (p=0.05) severe CP (p=0.04)

Duration of rhythmic EEG patterns in neonates:
new evidence for clinical and prognostic evidence of brief rhythmic discharges;
Oliveira AJ et al, Clin Neurophysiol, 2000; 111:1646

- 340 neonates (GA 30-40 wks):
  Brief rhythmic discharges (BRD <10 sec); Long RD >10 sec or no RD
- 210 no-RD; 19.7% only BRD and 18.5% at least one LRD
- clinical symptoms in only 16% of the BRD and 26% of the LRD
- BRD were associated with PVL and a poor outcome (p<0.01)

Seizure-associated brain injury in term newborns with perinatal asphyxia.

- N=33/90 infants (37%) with clinical seizures.
- Seizure severity was associated with increased lactate/choline in both the intervascular boundary zone (p < 0.001) and the basal nuclei (p = 0.011) when controlling for potential confounders of MRI abnormalities and amount of resuscitation at birth.
- The severity of seizures in human newborns with perinatal asphyxia is independently associated with brain injury and is not limited to structural damage detectable by MRI.
Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury; Glass HC et al; J Ped 09; 155:318-23

Table II. Predominant pattern of injury by seizure severity in 77 infants at risk for perinatal hypoxic-ischemic brain injury followed to age 4 years.

<table>
<thead>
<tr>
<th>Pattern of injury, n (%)</th>
<th>Severe seizures (n=11)</th>
<th>Mild/moderate seizures (n=14)</th>
<th>No seizures (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No injury</td>
<td>1 (9.1)</td>
<td>1 (7.1)</td>
<td>19 (36.5)</td>
</tr>
<tr>
<td>Basal nuc set pattern</td>
<td>6 (54.6)</td>
<td>6 (42.9)</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>Weshed pattern</td>
<td>4 (36.4)</td>
<td>7 (50.0)</td>
<td>29 (55.8)</td>
</tr>
</tbody>
</table>

*P < .001, Fisher exact test.

Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury; Glass HC et al; J Ped 09; 155:318-23

Table III: WPPSI-R FSIQ score at 4 years by seizure severity in 77 children at risk for perinatal Hypoxic-ischemic brain injury

<table>
<thead>
<tr>
<th>FSIQ score, mean(95%CI)</th>
<th>Severe seizures (n=11)</th>
<th>Mild/moderate seizures (n=14)</th>
<th>No seizures (n=52)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>unadjusted</td>
<td>64.7 (52.6 to 76.9)</td>
<td>83.1 (72.4 to 93.9)</td>
<td>100.2 (94.6 to 105.8)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>adjusted</td>
<td>67.2 (54.6 to 79.8)</td>
<td>82.7 (72.7 to 92.7)</td>
<td>96.9 (90.7 to 103.1)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Conclusions: clinical neonatal seizures in the setting of birth asphyxia are associated with worse neurodevelopmental outcome, independent of the severity of hypoxic-ischemic brain injury.

Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury; Glass HC et al; J Ped 09; 155:318-23

• Conclusions: clinical neonatal seizures in the setting of birth asphyxia are associated with worse neurodevelopmental outcome, independent of the severity of hypoxic-ischemic brain injury.

Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury; Glass HC et al; J Ped 09; 155:318-23

Post Neonatal Epilepsy (PNE) following aEEG detected neonatal seizures Toet MC et al; Pediatr Neurol 2005; 32:241-247

• PNE was especially common in children with basal ganglia injury
• A strikingly lower cumulative incidence of PNE was found in our study (9.5%), and in a study of Hellström-Westas (8.3%), both treating clinical and subclinical seizures
• Compared with an incidence of 20-50% in studies treating only clinical seizures (Clancy and Legido 1991; Brunquell 2002)

Conclusions Toet MC et al; Pediatr Neurol 2005;

Multicentre randomised study (8 Dutch and 3 Belgian Centres) SuSeQ (Subclinical Seizure Question)

aEEG +
1st subclinical seizure

A
Registration 48 hrs aEEG and impedance visible
Treatment of clinical + subclinical seizures (>2/hr).

B
Registration 48 hrs aEEG blinded Impedance visible
Treatment of clinical seizures + EEG 1/day
Aim and hypothesis: I

• How many seizure discharges will be missed in full-term neonates with HIE, when there is no continuous aEEG monitoring

• Does immediate treatment of electrographic seizures lead to a reduction of the total duration of seizure discharges

Aim and hypothesis: II

• Treatment of electrographic seizures leads to:
  – reduced risk of development of postneonatal epilepsy
  – improved neurodevelopmental outcome at 24 months

Methods: SuSeQue-study

• Randomized controlled multicentre trial

• 11 NICU’s in the Netherlands and Belgium

• Inclusion between November 2003 and March 2008

Methods

• aEEG monitoring using Olympic 6000 (Natus, US)

• Randomisation: first subclinical seizure confirmed on the aEEG

  – **Group A**: treatment of clinical and subclinical seizures
  
  – **Group B**: only treatment of clinical seizures (registration was blinded)

Methods

<table>
<thead>
<tr>
<th>Step</th>
<th>Treatment protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td><strong>Phenobarbitalone</strong>: 20 mg/kg, eventually another 10 mg/kg</td>
</tr>
<tr>
<td>Step 2</td>
<td><strong>Midazolam</strong>: loading dose of 0.05 mg/kg followed by continuous infusion of 0.15 mg/kg/hr, maximum of 0.2 mg/kg/hr. (When seizures were stopped for 24 hours tailed off to 0.1 mg/kg/hr and stop after 48 hours)</td>
</tr>
<tr>
<td>Step 3</td>
<td><strong>Lidocaine</strong>: Loading dose of 2 mg/kg followed by continuous infusion of 6 mg/kg/hr for 6 hours then 4 mg/kg/hr for 12 hours, then 2 mg/kg/hr for 12 hours. (always stop after 36 hours)</td>
</tr>
<tr>
<td>Step 4</td>
<td><strong>Clonazepam</strong>: loading dose of 2 mg/kg followed by continuous infusion of 0.1-0.5 mg/kg/day</td>
</tr>
<tr>
<td>Step 5</td>
<td>Experimental: pyridoxine 50 mg/kg</td>
</tr>
<tr>
<td>Step 6</td>
<td>Further treatment on clinician’s decisions</td>
</tr>
</tbody>
</table>

Entry criteria:

  – ≥ 37 weeks of gestational age
  – Admitted to the NICU within 24 hours with HIE and/or seizures

Criteria HIE:

  • Signs of intra-uterine asphyxia (late deceleration, meconium stained liquor)
  
  • Arterial cord blood pH < 7.10
  
  • Apgar score < 5 at 5 minutes
  
  • Delayed onset of spontaneous respiration
  
  • Multi organ failure
Methods

• MRI: 4-14 days
• T1, T2 and DWI
• Scoring system for basal ganglia, watershed areas and posterior limb of the internal capsule (PLIC) (score 0-11) (adapted from Barkovich et al)

Methods

Basal ganglia (BG)
1. Normal
2. Abnormal signal in thalamus
3. Abnormal signal in thalamus and lentiform nucleus
4. Abnormal signal in thalamus, lentiform nucleus, and periolandic cortex
5. More extensive involvement

Watershed (WS)
1. Normal
2. Single focal infarction
3. Abnormal signal in anterior or posterior watershed white matter
4. Abnormal signal in anterior or posterior watershed cortex and white matter
5. More extensive cortical involvement

PLIC
1. Myelination present
2. Myelination present but impaired
3. Absent

Results

Grade of HIE, AED use and mortality in both groups

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIE grade II</td>
<td>11 (58%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>HIE grade III</td>
<td>8 (42%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>AED &lt; 3</td>
<td>5 (26%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>AED ≥ 3</td>
<td>14 (74%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>died</td>
<td>6 (53%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>MRI</td>
<td>15 (79%)</td>
<td>11 (79%)</td>
</tr>
</tbody>
</table>

Results

Median duration of seizure discharges

Group A: 196 minutes
Group B: 503 minutes

Not significant
Results

Median duration of seizure discharges

Group A
HIE grade 2: 80 minutes
HIE grade 3: 257 minutes

Group B
HIE grade 2: 385 minutes
HIE grade 3: 1733 minutes

Not significant

Results

aEEG analysis group A:
• 8/19 infants treatment was appropriate
• 11/19 infants seizures existed for at least 2 hours, before 2nd or 3rd line AED was given

Median duration of seizure discharges

Treatment group A
appropriate: 37 minutes
insufficient: 248 minutes

P = 0.048

Results: MRI

• 26/33 infants had MRI
  – (15 in group A and 11 in group B)
• Median age 5.5 days (range 3-9)
• Median MRI score in both groups of 4

Results: MRI

Linear regression between seizure duration and MRI score

P < 0.001  P = 0.292  P = 0.001

Conclusions SuSeQue

• There is a trend for reduction in seizure duration, when treating clinical as well as subclinical seizures
• Treatment of subclinical seizures is associated with a lower MRI-abnormality score
• Benefit for long-term outcome and presence of PNE could not be shown in the small number of survivors

Conclusions

• **When**: neonatal seizures develop earlier in HIE than stroke or metabolic disorders.
• **What**: AEDs used at present are not successful and newer drugs (levetiracetam, topiramate, bumetanide) may be more effective
• **Why**: some evidence that not only SE but also (sub)clinical seizures have an adverse effect on long-term outcome