Modern assessment and monitoring of Brain Function in Neonates

background

Ipokrates Leuven sept 2012
Mona Tost

An international survey of EEG use in the neonatal intensive care unit.

- N=210: 124 Europe, 54 US.
- 90% had access to either EEG or aEEG monitoring; 51% had both.
- EEG was mainly interpreted by neurophysiologists (72%).
- aEEG was usually interpreted by neonatologists (80%).
- Only 9% of respondents reported that they felt 'very confident' in their ability to interpret aEEG/EEG with 31% reporting that they were 'not confident'.
- Half had received no formal training in EEG.
- There is an urgent need for a structured and appropriately targeted training programme in EEG methodologies and EEG interpretation for neonatal intensive care unit staff.

Guidelines for continuous monitoring in the fullterm infant

- “Perinatal asphyxia”
- Neonatal seizures and/or apneas
- Metabolic disorders
- Meningo-encephalitis
- Post-surgery, especially cardiac surgery (together with NIRS)
- Muscle paralysis

Imaging
Neurophysiology

- Ultrasound (CT)/MRI
- Structure
- (a)EEG
- Evoked potentials
- Function

aEEG/CFM

- Immediately available
- Long registration
- No detail
- Pattern recognition

EEG

- On appointment
- Short registration
- A lot of detail
- Interpretation difficult

aEEG

- Filtered (2-15 Hz)
- amplification
- compressed (6 cm/hr)
- Semilogarithmic scale
- 1 channel (2 parietal leads)
- 1 channel for impedance
amplitude integrated EEG

signal filtered

amplitude integrated EEG

signal rectified, smoothed

amplitude integrated EEG

signal compressed in time

amplitude integrated EEG

signal compressed in time

amplitude integrated EEG

signal compressed in time
The predictive value of early neurological examination in neonatal hypoxic-ischaemic encephalopathy and neurodevelopmental outcome at 24 months.


- N=57 The clinical and electrographic signs of HIE evolve over the first days of life.
- Amiel-Tison Neurological Assessment at Term (ATNAT) first 3 days neurodevelopmental outcome at 24 months.
- Persistence of abnormal neurological signs correlates significantly with adverse outcome.
- The later a neonatal neurological examination was performed, the better its predictive ability.

Early EEG findings in hypoxic-ischemic encephalopathy predict outcomes at 2 years.


- CONCLUSIONS:
  Early EEG is a reliable predictor of outcome in HIE.
  A normal or mildly abnormal EEG results within 6 hours after birth were associated with normal neurodevelopmental outcomes at 24 months.
Conclusions

- 20% of full-term infants with a very poor BG pattern < 6 hrs after birth show recovery within the first 24 hrs.

- 61% of these infants with early recovery have a normal or mildly abnormal outcome

- aEEG should be continued for a period of at least 24 hrs even in infants with an initially severely abnormal background pattern

Prediction of outcome

- 96.1% of newborns who showed normal SWC ≤ 36 hrs had a good neurodevelopmental outcome

- Only 20% of those who developed persistently abnormal SWC > 36 hrs had a good outcome.

EEG and timing of brain injury

Watanabe et al, Brain Dev 1999

Anticonvulsant drugs

- phenobarbital (94.1%)
- lidocaine (58.8%)
- midazolam (43.1%)
- clonazepam (39.2%)
- phenytoin (35.3%)

Sleep-wake cycling in newborns with HIE; Osredkar et al; Pediatrics, 2005;115:327-332
Late Onset seizures: secondary energy failure?

- Seizures can first develop after the first 24-48 hours
- This is usually noted following recovery of a severely depressed BG pattern, but can also be seen following an initially normal BG pattern
- aEEG recording should therefore be continued for at least 48 hrs

• aEEG is useful for selection of patients for intervention studies, such as Hypothermia
• However:
  - spontaneous recovery of a poor background pattern does occur, also without the use of hypothermia
  - deterioration of a good background pattern can also occur, probably due to secondary energy failure

Selection of candidates using the Classification of: al Naqeeb (Pediatrics 1999)

<table>
<thead>
<tr>
<th>Category</th>
<th>Upper Margin</th>
<th>Lower Margin</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>&gt; 10 µV</td>
<td>&gt; 5 µV</td>
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<tr>
<td>Moderately abn</td>
<td>&gt; 10 µV</td>
<td>≤ 5 µV</td>
</tr>
<tr>
<td>Severely abn</td>
<td>&lt; 10 µV</td>
<td>≤ 5 µV</td>
</tr>
</tbody>
</table>

Be Careful!

To use quantitative data and alternative electrodes positions for inclusion criteria for intervention
Questions raised

- Effect of hypothermia on
  - background pattern?
  - rate of recovery of background pattern?
  - time of onset of neonatal seizures?
  - visualisation of changes on MRI, in particular DWI changes

Table 3. Difference in aEEG voltage during last 6 h of cooling and first 6 h of rewarming

<table>
<thead>
<tr>
<th>aEEG (cooling/rewarmed)</th>
<th>Difference (µV)</th>
<th>No of samples</th>
<th>S.D. (µV)</th>
<th>Significanc e (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper margins</td>
<td>−0.93</td>
<td>88</td>
<td>2.77</td>
<td>0.08</td>
</tr>
<tr>
<td>Lower margins</td>
<td>0.04</td>
<td>88</td>
<td>1.31</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Conclusion: Mild hypothermia to 34 °C for up to 48 hrs did not influence the aEEG suggesting that cerebral monitoring with aEEG is possible during mild hypothermia

Conclusions (1)

- aEEG does give valuable information at the start of, during hypothermia, and following rewarming about:
  - background pattern at enrollment
  - recovery of background pattern during hypothermia
  - development of (electrographic) seizures

Conclusions (2)

- aEEG is maybe too strict in selecting infants for hypothermia and may miss those few infants who subsequently develop secondary energy failure
The prognostic value of early aEEG in asphyxiated infants undergoing systemic hypothermia treatment.


CONCLUSION:
Among asphyxiated infants treated with HT, only those who had aEEG abnormalities persisting at and beyond 24 h after birth showed poor neurological outcome at 1 year.

M. Thoresen, L. Helstrom-Westas, X. Liu, L. de Vries
Pediatrics 2010;126:e131-e139

• Single centre
• 74 infants with NT and HT
• All aEEG
• Outcome Bayey-II at 18 months
• HT 40% death or disability
• NT 65% death or disability

Time to regain normal aEEG trace is shown on the y-axis, and infants who never regained a normal trace within the recording period are plotted on top of the figure.


Conclusion

• Pattern recognition method is superior to the voltage method for correct prediction in infants with a moderately abnormal trace
• With HT treatment, early aEEG does not predict outcome, however early recovery to a good trace predicts good outcome


**Conclusions**

A decreased seizure burden was seen in neonates with moderate HIE who received cooling.

This finding may explain some of the therapeutic benefits of cooling seen in term neonates with moderate HIE.

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**More literature on HIE and aEEG**

aEEG and seizure detection

Electrographic Seizures
- n=9 children
- 526 seizures

Clinical signs present on Video
- n=179 seizures (34%)

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

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

Interobserver agreement in neonatal seizure identification
- Twenty video clips (11 seizure, 9 nonseizure) were evaluated by 91 doctors and 46 other professionals
- Clonic seizures were correctly identified most frequently (range 36.5-95.6% of observers)
- Subtle seizures were poorly identified (range 20.4-49.6% of observers)
- The interobserver agreement (Kappa) for doctors and other health care professionals was poor at 0.21 and 0.29, respectively.
- Agreement with the correct diagnosis was also poor at 0.09 for doctors and -0.02 for other healthcare professionals.

Lack of clinical-electrical correlation
- Mizrahi and Kellaway: phenobarbitone administration often leads to cessation of only clinical seizures
- some clinical seizures may originate in deep cerebral structures or brainstem structures and are therefore not detected using surface electrodes
- clonic seizures can be due to “brainstem release phenomena”
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)

No data available so far whether treatment of subclinical seizures is beneficial

Correlation aEEG / EEG
epileptiform activity
aEEG detects epileptiform activity in 80% of children
aEEG misses frontal, occipital low amplitude seizure discharges no false positive epileptiform activity
Toet et al; Pediatrics 2002; 109:772-779

Accuracy of amplitude integrated EEG in a neonatal cohort.

• Sens for presence of seizures by aEEG: 80%, spec 50%.
• seizures were overdiagnosed by aEEG (63.6% vs 45.5% for sEEG p=0.045).
• Discontinuity of BG activity: sens (88.6%), spec (54.5%).

EEG monitoring of neonatal seizures
aEEG problems
• artifacts
• extra central location
• amplitude
• duration
• subjectivity

Neonatal seizures, number, duration and location

<table>
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<tr>
<th>pt</th>
<th>n</th>
<th>duration</th>
<th>P2-1</th>
<th>T4-3</th>
<th>Cz</th>
<th>C3</th>
<th>O2-1</th>
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<tr>
<td>1</td>
<td>1</td>
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<td>+</td>
<td></td>
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<tr>
<td>2</td>
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<td>12</td>
<td>79.5 (43-150)</td>
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<td>14</td>
<td>5</td>
<td>88.6 (29-156)</td>
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<td>16</td>
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<td>11</td>
<td>12</td>
<td>4</td>
<td>5</td>
<td>0.4</td>
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</table>

Characterization of neonatal seizures by conventional EEG and single-channel EEG
R Shethaas and R Clancy, Clin Neurph; 118(10):2156-61

• 851 seizures from 125 cEEG’s
• Minimum seizure duration: 10 sec

• 81% of NS from central-temporal or midline electrodes
• 78% of NS appeared in C3-C4 (~aEEG)
Characterization of neonatal seizures by conventional EEG and single-channel EEG

- NS burden is very high
- Median duration of C3-C4 seizures: 44 sec
- Seizures briefer and lower amplitude C3-C4
- Only 5% NS frontopolar electrodes
- 94% of EEG records having at least 1 seizure C3-C4

Automated neonatal seizure detection

Automated neonatal seizure detection: still a long way to go
An evaluation of automated neonatal seizure detection methods.
 Faul S Clinical Neurophysiology 2005; 116: 1533-1541

- 3 automated algorithms (Gotman, Liu and Celka)
- Sensitivity 62.5, 42.9 and 66.1% with a specificity of 64.0, 90.2 and 56.0%.

- Conclusion: level of performance achieved by the seizure detection algorithms are not (yet) high enough for clinical use.

Heart rate based automatic seizure detection in the newborn

- Sixty-two time-domain and frequency-domain features were extracted from the neonatal heart rate signal
- Classified using a sophisticated support vector machine (SVM) scheme

- Overall:
  perform well in some patients (2 out of 14)
  but performed poorly when tested on the entire group.

EEG-based neonatal seizure detection with Support Vector Machines

- A machine learning algorithm (SVM) is used as a classifier to discriminate between seizure and non-seizure EEG epochs.
- Two post-processing steps are proposed to increase both the temporal precision and the robustness of the system.
- The resulting system is validated on a large clinical dataset of 287 h of EEG data from 17 full-term newborns with seizures.
Detection of seizures of different duration by the SVM-based seizure detection system at 1 FD/h. The number of seizures in each time category is 72, 182, 240, and 197.

- Detection rate of 89% with one false seizure detection per hour, 96% with two false detections per hour, or 100% with four false detections per hour.
- An analysis of errors revealed sources of misclassification in terms of both missed seizures and false detections.

**ACCURACY OF BEDSIDE AEEG IN COMPARISON WITH SIMULTANEOUS CONTINUOUS CONVENTIONAL EEG FOR SEIZURE DETECTION IN TERM INFANTS**

**Shah DK et al, Pediatrics 2008; 121: 1146-1154**

<table>
<thead>
<tr>
<th>Condition</th>
<th>sens. %</th>
<th>spec. %</th>
<th>PPV %</th>
<th>NPV %</th>
<th>k</th>
<th>p</th>
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</thead>
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<tr>
<td>2-ch aEEG + raw EEG agreed</td>
<td>76</td>
<td>78</td>
<td>78</td>
<td>78</td>
<td>0.67</td>
<td>&lt;0.00</td>
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<td>85</td>
<td>79</td>
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<td>1-ch aEEG</td>
<td>41</td>
<td>66</td>
<td>55</td>
<td>66</td>
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<tr>
<td>rater 1</td>
<td>27</td>
<td>98</td>
<td>92</td>
<td>98</td>
<td>0.31</td>
<td>0.01</td>
</tr>
<tr>
<td>rater 2</td>
<td>44</td>
<td>83</td>
<td>72</td>
<td>83</td>
<td></td>
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</table>

* K ccEEG: 0.84 (p< 0.001)

Seizures missed:
- Slow sharp waves of occipital origin
- 9 false-positive results of 351 hours recording
- Muscle, electrode, patting artifact

* Median period of recording: 18.6 hours
* 351 hours of data

**SHAH DK ET AL. PEDIATRICS 2008; 121: 1146-11**
A pilot study of continuous limited-channel aEEG in term infants with encephalopathy.

Lawrence et al., J Pediatr. 2009 Jun;154(6):835-41

- **CONCLUSIONS:**
  Monitoring for seizures with limited-channel aEEG can be accurately interpreted, compares favorably with cEEG, and is associated with a trend toward reduced seizure burden.

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**One or more channels?**

- Is one channel aEEG sufficient as a MONITOR in the NICU and especially in full-term infants with global hypoxia-ischaemia?

- Is there benefit in using a 2-channel aEEG
  - in every high risk infant
  - in a selected group of children with a unilateral parenchymal lesion (MCA/HPI)

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**Conclusion**

- In general: No major differences were found between seizure detection with 1 or 2 channel aEEG.

- In subgroup with unilateral lesions: 2 ch. additional information: more seizures on affected side, sometimes different BGP

Van Rooij et al, Arch Dis Child Fetal Neonatal Ed. 2009

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**Neurodevelopmental outcome in full term infants with SE detected with aEEG**

- 56 term infants with SE during a 12.5 year period

- The incidence of SE in our population of full-term infants with seizures was 18%.

- 42 (75%) poor outcome (35 died and 7 survived with a severe disability)

- 14 infants were normal at follow-up

Van Rooij et al, Pediatrics 2007; 120: e354-e363

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**The distribution of the total duration of SE in minutes for 41 infants in whom the duration could be calculated with certainty**

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**BGP before and after status epilepticus**

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Status epilepticus

- poor outcome: BGP was abnormal before the SE in 50% and in 71% after the SE; good outcome with 14% before and 7% after the SE ($p<0.05$).

- HIE ($n=48$) significant difference in BGP as well as in duration of the SE between poor outcome compared to good outcome.

- hemorrhage or PAS: 57% of infants with a SE was not controlled with AEDs, compared to 21% in infants with HIE (not significant).

Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury.

Seizures are associated with brain injury severity in a neonatal model of hypoxia-ischemia
Bjorkman et al.; Neuroscience 2010

Effect of treatment of Subclinical Neonatal Seizures Detected with aEEG: Randomized Controlled trial

Effect of treatment of Subclinical Neonatal Seizures Detected with aEEG: Randomized Controlled trial


Hypothermia N=56; video EEG through cooling and rewarming, MRI median of 5 days.
Seizures: n=17 (30%), 5 SE

Moderate-severe injury:
- more common in newborns with seizures (relative risk, 2.9;95%CI, 1.2-4.5;P = .02)
- in all 5 newborns with status epilepticus
- seizures multifocal and of later onset, and more recurrent seizures after treatment with 20 mg/kg phenobarbital.
- subclinical seizures were as likely to have injury as those with seizures with a clinical correlate (57% vs 60%).

Conclusion
Seizures represent a risk factor for brain injury in the setting of therapeutic hypothermia, especially in neonates with status epilepticus, multifocal-onset seizures, and a need for multiple medications.
However, 40% of our neonates were spared from brain injury, suggesting that the outcome after seizures is not uniformly poor in children treated with therapeutic hypothermia.
More literature on seizures in HIE


aEEG in premature infants

Mona Toet
Lena Helström-Westas

Continuous activity and maturation

Interburst intervals and maturation

Strongest maturational aEEG feature – rise of the lower border amplitude

Normal preterm aEEG

(Heidström-Westas, Rosén, de Vries, Greisen. Neoreviews 2006)

- Continuous (C)
- Discontinuous (DC)
- Burst-suppression (BS)
  - Burst density >100/h (BS+)
  - Burst density <100/h (BS−)
- Low voltage (LV)
- Flat (FT, isoelectric)
Normal aEEG's at different gest. ages
(Thornberg & Thiringer 1990, Kühle et al 1999)

aEEG/CFM Scoring System
(Burdjalov et al, Pediatrics 2003)

Averaged IBI (6-72 h) and 2-y outcome
(Wikström et al, Acta Paediatr 2008)

<table>
<thead>
<tr>
<th></th>
<th>No handicap (n=8)</th>
<th>Handicap (n=8)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBI, seconds</td>
<td>8.7 (7.1-23.2)</td>
<td>11.8 (9.6-14.1)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

- N = 16 infants with GA 24-28 w (median 25.4)
- aEEG first 72 hours
- Follow up at 2 years: Neurologic optimality score, Bayley II, Schellfz

Early markers of poor short term outcome in infants with GA < 29 w
(Bowen et al, Pediatr Res 2010)

N=65 infants, aEEG < 48 h,
Markers of poor outcome (died/IVH 3-4):
- continuity < 80% at 10 µV
- no SWC and baseline variability <2 µV

aEEG continuity and mean arterial blood pressure
(West et al, Pediatr Res 2006)

Plasma glucose and IBI in extremely preterm infants
(Wikström et al, Pediatrics 2011)
Carbon dioxide and EEG

Increasing PaCO₂ → increasing IBI
Decreasing PaCO₂ → increasing relative delta activity
Strongest effect on day 1, absent day 3

Carbon dioxide and IBI
(Wikström et al, Pediatrics 2011)

Conclusion: aEEG/EEG in preterm infants
- aEEG/EEG changes with maturation (continuity, sleep wake cycling)
- Brain injury, physiological changes and medications are associated with aEEG/EEG alterations
- Presence of seizures is associated with brain injury
- Early aEEG/EEG is predictive of outcome in preterm infants, but the accuracy is lower than in term infants

aEEG in other conditions

Amplitude integrated electroencephalographic activity in infants with congenital heart disease before surgery
Ter Horst et al. Early Hum Dev. 2010 Dec;86(12):759-64.

The prognostic value of amplitude integrated EEG in neonatal sepsis and/or meningitis

AEEG in Newborns with Inborn Errors of Metabolism.
Olischar et al. Neonatology 2012;102:203-211