Current Concepts on the Value of aEEG in Premature Infants

Part II: research/concepts for the future

K. Klebermass, M. Olischar
A. Pollak, M. Weninger
Department of Pediatrics, Division of Neurology
Medical University Vienna

Background

Main concept for the future of aEEG in preterm infants should be the same as in term infants

being of prognostic value

Background

- Concepts for the future
  - Combining neurophysiology (=function) and brain imaging (=morphology)

- Main Questions
  - Is early assessment of neurophysiology helpful in determining neurodevelopmental prognosis in preterm infants?
  - Is assessment of changes during IVH and posthemorrhagic hydrocephalus (PHH) helpful in determining need/timepoint for clinical intervention?
  - Individualized therapy of PHH
Background
There is no doubt that an early estimate of neurodevelopmental outcome will be of great value in the care of preterm patients and their parents.

is aEEG meeting this demand??

Research Data
Our aim was to analyse (with the following study)
if there was a correlation between aEEG-pattern in the first two weeks of life of preterm infants born < 30 weeks GA and their neurodevelopmental outcome at 3 years of age
and
if aEEG can therefore be used as an early prognostic tool

Research Data
- between 2000-2002 consecutively 284 preterm infants < 30 wks of gestation were analyzed/measured once a week by aEEG
- 148/284 infants (lost to follow-up, transfer) were evaluated at the (corrected) age of 3 years by assessment of Bayley Scales of Infant Development and clinical neurological assessment
- 143/148 infants were analyzed by aEEG within the first 14 days of life
Patient and Methods

- Only tracings of the first two weeks of life were included for analysis in this study.
- Tracings were evaluated visually and classified by pattern recognition according to our method previously published (Pediatrics 2004).
  - Mainly according to:
    - Background activity - percentage of continuous and discontinuous patterns
    - Appearance of sleep-wake-cycling
    - Occurrence of seizure activity

Methods

In preterm infants three „physiological patterns“ exist:
- Continuous pattern
  \[6.09 \pm 1.171 \text{ - } 31.91 \pm 11.99 \text{ } \mu V\]
- Discontinuous patterns
  - Burst Suppression Pattern
    \[2.32 \pm 0.835 \text{ - } 26.19 \pm 12.13 \text{ } \mu V\]
  - Discontinuous Pattern
    \[4.12 \pm 0.966 \text{ - } 30.40 \pm 11.53 \text{ } \mu V\]

Methods

Analysis of the tracings:
- Every epoch of ten minutes was visually classified in one of these background patterns (according to the amplitude).
- Evaluation of the distribution of background patterns / percentages was measured and compared to age-adequate reference values.
- If visually not clearly classified -> measuring of amplitudes.
**Methods**

aEEG-background patterns – Reference values
(Olischar et al, Pediatrics 2004)

<table>
<thead>
<tr>
<th>Type of Pattern</th>
<th>Normal</th>
<th>5th</th>
<th>25th</th>
<th>75th</th>
<th>95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of discontinuous low voltage pattern (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gestational Week 24 or 25</td>
<td>11</td>
<td>55.6</td>
<td>46.2</td>
<td>70</td>
<td>85.5</td>
</tr>
<tr>
<td>Gestational Week 26 or 27</td>
<td>38</td>
<td>34</td>
<td>33.3</td>
<td>59</td>
<td>79.9</td>
</tr>
<tr>
<td>Gestational Week 28 or 29</td>
<td>26</td>
<td>7.1</td>
<td>0</td>
<td>32</td>
<td>82.6</td>
</tr>
<tr>
<td>Duration of discontinuous high voltage pattern (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational Week 24 or 25</td>
<td>11</td>
<td>39.9</td>
<td>11.5</td>
<td>17.6</td>
<td>54</td>
</tr>
<tr>
<td>Gestational Week 26 or 27</td>
<td>38</td>
<td>56.4</td>
<td>5.9</td>
<td>31.4</td>
<td>65</td>
</tr>
<tr>
<td>Gestational Week 28 or 29</td>
<td>26</td>
<td>51.8</td>
<td>2.9</td>
<td>26.2</td>
<td>74</td>
</tr>
<tr>
<td>Duration of continuous pattern (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>11</td>
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<td>0</td>
<td>8.7</td>
<td>14.8</td>
</tr>
<tr>
<td>Gestational Week 26 or 27</td>
<td>38</td>
<td>5.9</td>
<td>0</td>
<td>21</td>
<td>56.6</td>
</tr>
<tr>
<td>Gestational Week 28 or 29</td>
<td>26</td>
<td>16.6</td>
<td>0</td>
<td>67</td>
<td>76.9</td>
</tr>
</tbody>
</table>

**Methods**

- Definition of sleep-wake-cycles: cyclical, sinusoidal variation of amplitude and continuity of aEEG-activity,
  Quiet-sleep episode approximately 20 minutes

**Methods**

- Definition „seizure activity“
  - Saw-tooth-pattern
  - Single seizures
  - Repetitive seizures
Methods
- Definition “normal aEEG”
  - Age-adequate distribution of background patterns
  - Appearance of Sleep-Wake-Cycles
  - No seizure activity

Methods
- “abnormal aEEG”
  - Flattening/more discontinuity - higher percentage of discontinuous patterns according to age
  - No Sleep-Wake-Cycles
  - Occurrence of seizure activity
  - If 2/3 = severely abnormal aEEG
  - If only 1/3 = moderately abnormal aEEG

Methods
- Definition “normal Outcome”
  - no neurological and/or neurosensory impairment
  - Bayley Scales of Infant Development
    - Mental Developmental Index
    - Psychomotor developmental Index
      - MDI and PDI > 85
**Methods**
- "Severely impaired"
  - Clinical neurological impairment (CP)
  - and/or severe neurosensory impairment (deafness, blindness)
  - MDI and/or PDI < 70
  - death
- "moderately impaired"
  - Mild clinical neurological impairment (CP)
  - and/or mild neurosensory impairment
  - and MDI and/or PDI > 70 < 85

**Methods**

Statistical analysis
- positive predictive value, negative predictive value; Sensitivity and Specificity

for showing a normal neurodevelopmental outcome following a normal aEEG tracing within the first two weeks of life (=true positive)

**Results**

<table>
<thead>
<tr>
<th>Outcome 3 yrs</th>
<th>aEEG normal</th>
<th>aEEG mildly abnormal</th>
<th>aEEG severely abnormal</th>
<th>Sleep-Wake-Cycles</th>
<th>Seizure activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (N=61)</td>
<td>93% (57/61)</td>
<td>5% (3/61)</td>
<td>2% (1/61)</td>
<td>90% (60/61)</td>
<td>3% (2/61)</td>
</tr>
<tr>
<td>Mildly impaired (n=21)</td>
<td>48% (10/21)</td>
<td>38% (8/21)</td>
<td>14% (3/21)</td>
<td>76% (16/21)</td>
<td>0% (0/21)</td>
</tr>
<tr>
<td>Severely impaired (n=61)</td>
<td>8% (5/61)</td>
<td>7% (4/61)</td>
<td>85% (52/61)</td>
<td>43% (26/61)</td>
<td></td>
</tr>
</tbody>
</table>
Results - Summary

<table>
<thead>
<tr>
<th></th>
<th>Outcome 3 yrs normal</th>
<th>Outcome 3 yrs impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=61</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>aEEG normal</td>
<td>aEEG abnormal</td>
</tr>
<tr>
<td></td>
<td>93% (57/61)</td>
<td>7% (4/61)</td>
</tr>
<tr>
<td></td>
<td>Existing SWC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>98% (60/61)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>aEEG normal</td>
<td>aEEG abnormal</td>
</tr>
<tr>
<td></td>
<td>18% (15/82)</td>
<td>82% (67/82)</td>
</tr>
<tr>
<td></td>
<td>Existing SWC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28% (23/82)</td>
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</tbody>
</table>

Results - Comparison to CUS

<table>
<thead>
<tr>
<th></th>
<th>Outcome 3 yrs normal</th>
<th>Outcome 3 yrs impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=61</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CUS normal</td>
<td>CUS abnormal</td>
</tr>
<tr>
<td></td>
<td>86% (53/61)</td>
<td>14% (8/61)</td>
</tr>
<tr>
<td></td>
<td>aEEG normal</td>
<td>aEEG abnormal</td>
</tr>
<tr>
<td></td>
<td>93% (57/61)</td>
<td>7% (4/61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CUS normal</td>
<td>CUS abnormal</td>
</tr>
<tr>
<td></td>
<td>32% (26/82)</td>
<td>68% (56/82)</td>
</tr>
<tr>
<td></td>
<td>aEEG normal</td>
<td>aEEG abnormal</td>
</tr>
<tr>
<td></td>
<td>18% (15/82)</td>
<td>82% (67/82)</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

Results

- Positive predictive value for showing a normal Outcome at the age of 3 yrs after having a normal aEEG tracing within the first two weeks of life
  - PPV 0.79
  - NPV 0.94
  - Sensitivity 0.93
  - Specificity 0.81
Results

- Sensitivity is even higher looking only at appearance of sleep-wake-cycling within the first two weeks of life
  - PPV 0.72
  - NPV 0.98
  - Sensitivity 0.98
  - Specificity 0.71

Results CUS

- Positive predictive value for showing a normal outcome at the age of 3 yrs after having a normal CUS
  - PPV 0.67
  - NPV 0.87
  - Sensitivity 0.86
  - Specificity 0.68

Literature

- Predictive value of early neuroimaging, pulsed Doppler and neurophysiology in full term infants with hypoxic-ischaemic encephalopathy Eken et al., 1995
  - PPV of aEEG 0.84
  - PPV of SEP 0.81 both better than CUS
- Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm. Rademakers et al. „poor correlation“ of CUS and MRI of 6yr outcome (only within severely impaired)
- Neonatal brain magnetic resonance imaging before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants. Memel et al.
  - MRI Sens. 71%, Spec.91% at term age for prognosis of CP.
  - CUS Sens 43%, Spec. 82%
Conclusion

aEEG-pattern during the first two weeks of life in preterm infants below 30 weeks of gestational age correlates with neurodevelopmental outcome at three years of corrected age and can therefore be used as an early prognostic tool.

Value in IVH/PHH

Early prediction of outcome with aEEG in preterm infants with large intraventricular hemorrhages

Hellström-Westas et al., Neuropediatrics 2001

- Depression of aEEG background and depression correlates with the degree of IVH
- 64 infants, first week of life
- Bursts/h were predictive of outcome - even in the first three days of life

Value in IVH/PHH

Background patterns and sleep-wake cycles on amplitude-integrated electroencephalography in preterms younger than 30 weeks’ gestational age with peri-/intraventricular haemorrhage.

Olischar et al, Acta Paediatrica 2007

- Decrease of continuous activity, increase of seizure activity and decrease of sleep-wake-cycles in infants with IVH
- Later onset of sleep-wake-cycles in infants with IVH (even low grade bleeding)
Future clinical value in PHH?

- Prospective study
  - Evaluation of changes of aEEG activity with progressive posthemorrhagic hydrocephalus
    - CSF drainage in PHH leads to improvement of aEEG activity
    - Is this a new approach for optimizing the timing of intervention?

Results - PHH

- 40/723 infants acquired IVH
- 19/30 (IVH>II) developed PHH
- 12/19 needed CSF drainage and therefore fulfilled inclusion criteria

Results - PHH

- External ventricular drainage was inserted when clinical signs of elevated intracranial pressure appeared or ventricular width was >4mm of 97th percentile of ventricular index according to Levene
- aEEG was obtained every second day after IVH was evident
- Statistical analysis was done by calculation of the differences in prevalence of the different background patterns before and after intervention
Results - PHH

- 8/12 infants showed ventricular width >4mm>97th percentile at the time of intervention
- 2/12 showed elevated (<0.85) RI in Doppler sonography
- 12/12 showed abnormal aEEG patterns before intervention (according to background activity, appearance of sleep-wake-cycles, occurrence of seizure activity)

Results - PHH

Major improvement in background pattern was seen (11/12) at a mean of 4 days (range 2-8 d)
- Continuous pattern increased by (mean) 41.6% (p=0.0015)
- Discontinuous pattern decreased by 23.4% (p=0.03)
- Burst Suppression pattern decreased by 18% (n.s.)

Results - PHH

With regard to sleep-wake-cycles an improvement (from no or immature to fully developed SWC) could be detected in 9/12 infants.
Results - PHH
Preterm infant; 27+5 wks GA; IVH IV left, II right; PHH

<table>
<thead>
<tr>
<th>Rec</th>
<th>Day</th>
<th>BS</th>
<th>Disc.</th>
<th>cont</th>
<th>proc.</th>
<th>med.</th>
<th>RI</th>
<th>ventr. size</th>
<th>ventr. index</th>
<th>EVD</th>
<th>no</th>
<th>yes</th>
<th>0,8</th>
<th>14,3/11,3mm</th>
<th>&gt;97.perc.</th>
<th>no</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>25%</td>
<td>47%</td>
<td>20%</td>
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<td>no</td>
<td>0.8</td>
<td>4.3/11.3mm</td>
<td>97.perc.</td>
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<tr>
<td>2</td>
<td>10</td>
<td>6%</td>
<td>100%</td>
<td>3%</td>
<td>yes</td>
<td>no</td>
<td>0.8</td>
<td>4.5/12.2mm</td>
<td>97.perc.</td>
<td>no</td>
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<tr>
<td>3</td>
<td>12</td>
<td>67%</td>
<td>21%</td>
<td>16%</td>
<td>yes</td>
<td>yes</td>
<td>0.8</td>
<td>5.1/15.2mm</td>
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<tr>
<td>4</td>
<td>14</td>
<td>7%</td>
<td>50%</td>
<td>37%</td>
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<td>5</td>
<td>16</td>
<td>6%</td>
<td>29%</td>
<td>65%</td>
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<td>2.6/11mm</td>
<td>97.perc.</td>
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</tr>
</tbody>
</table>

Increase of burst suppression pattern from 33 to 63% (in 7 days) before intervention and fall to 7% 2 days after intervention
Decrease of continuous pattern from 20% to 16% (in 7 days) before intervention and increase to 37% 2 days after intervention
Note: occurrence of seizure activity and loss of sleep-wake-cycling before intervention

Results - PHH
26 wks GA, 700g
Apgar 6/8/9
IVH II on both sides – posthemorrhagic hydrocephalus

Day 12:
- Loss of sleep-wake-cycling;
- Increase in discontinuous low voltage pattern (20 to 90%);
- Decrease in continuous pattern (30 to 0%)

Results - PHH
RI 0.95
Ventricular width
- Right 12.7mm
- Left 14.8mm

3 days after insertion of external ventricular drainage
Increase in continuous activity (0 to 82%) and re-occurrence of sleep-wake-cycling
Conclusion

- aEEG may be of help in the future for individual therapeutic management of infants with posthemorrhagic hydrocephalus and may minimize secondary injury due to prolonged periods of elevated intracranial pressure.

Summary

Future concepts for aEEG in preterm infants

- Neurophysiological „screening“
- Prognostic value
- Guidance of therapeutic concepts

- In all preterm infants
- Especially in preterms with IVH and PHH

Future - Outlook

Combination of neurophysiological (=function) and imaging (= morphology)

Longitudinal measurings (e.g., on a weekly basis) and combination of function and morphology might even further improve prognostic value.