Neonatal EEG, Seizures and Epilepsy Syndromes

Introduction
- Over the past several decades great progress has been made in neonatal-perinatal medicine
- Survival of premature infants < 1 Kg is common
- Neonatal EEG presents some of the most difficult challenges in EEG interpretation
  - Acquisition is more difficult
  - Numerous features that change almost week to week
  - Many feature have different implications than in older children and adults

Purpose and Utility of Neonatal EEG
- Provides useful information that reflects the function of the neonatal brain
  - assist in determining brain maturation
  - measuring functional integrity of the immature cortex and its connections
  - existence of potentially epileptogenic foci or ongoing seizures
- Useful in assessing prognosis for neonates at risk for neurological sequelae

Objectives
- To review the features of electrocerebral maturation in the pre-term infant
- To review the features of electrocerebral maturation in the term neonate
- To highlight the important clinical aspects of neonatal seizures
Technical Considerations

- Challenges:
  - ICU setting
  - Poor cooperation
  - Small head
  - Critically ill
  - Multiple organs being monitored
    • unusual artifacts
    • difficulty reaching infant's head

Electrodes

- Minimum of 16 electrodes
- Standard 10-20 system
  - combined longitudinal/transverse montage
  - Frontal-temporal, frontal-central, temporal-occipital, and central-occipital longitudinal measurements are double distance
- Use of a single montage throughout recording

Technical Considerations

Technique – Physiological Leads

- Placed to aid in determination of state
  - EOG
    • Helpful in active sleep
  - EMG
    • Differentiating subcortical or peripheral myoclonus from movements associated with epileptiform activity
  - Respiratory monitor (chest wall and/or nasal airflow)
    • Slow and regular patterns of quiet sleep
    • Regular fast patterns of active sleep
  - ECG
    • Left and right arms
    • Pulse and ballistocardiographic artifact

Technique - Recording

- 60 minutes or more - recording of at least one change in state
  - Typically 50-60 minutes to cycle through 3 stages
- Consensus regarding paper speed not established
  - 15 mm/s most common
  - Facilitate delta activity which is the dominant frequency
  - Enhance asymmetries/asynchronies

Neonatal EEG Amplifier Settings

<table>
<thead>
<tr>
<th>Channel</th>
<th>LFP (mV)</th>
<th>HPF (mV)</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOG</td>
<td>0.3-1</td>
<td>50</td>
<td>1 pA/mV</td>
</tr>
<tr>
<td>DOG</td>
<td>1</td>
<td>50</td>
<td>1 pA/mV</td>
</tr>
<tr>
<td>DCG</td>
<td>5</td>
<td>70</td>
<td>Variable</td>
</tr>
<tr>
<td>Resp Min</td>
<td>0.1</td>
<td>15</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Legend: EOG = electro-oculogram, DOG = electro-oculogram, EOG = electro-oculogram, DOG = electro-oculogram, Resp = respiratory, LFP = low frequency filter, HPF = high frequency filter.
General Principles for Analysis

Approach:
- Knowledge of the gestational age and topography of the infant’s head
- Identification of artifacts in the EEG
- Identification of sleep and wake states
- Feature extraction
- Classification of the record as normal or abnormal and clinical correlation provided to clinician

Conceptual Age and Topography

- Accurate estimate of CA
- Description of skull and scalp topography
  - Altered interelectrode resistance/attenuate the recording
  - Scalp swelling and other forms of trauma
  - Meningocele
  - Subdural or epidural fluid collections
  - Skull fractures
    - Low-resistance pathway for electric fields and result in increased voltage
    - Distorted cranial vaults (common after birth trauma) also alter the topography of the EEG.

Artifact Rejection

| Cardiac | Cardiac
|---------|---------|
| Respiratory, flutter, and tremor | Respiratory, flutter, and tremor
| Vertical, horizontal, and rotary head movements | Vertical, horizontal, and rotary head movements
| Electrode “pops” and fontanelle-related pulsations | Electrode “pops” and fontanelle-related pulsations

| Head | Head
|------|------|
| Electrode “pops” and fontanelle-related pulsations | Electrode “pops” and fontanelle-related pulsations
| Face | Face
| Grosskinesthesia, eye movements, and blinks | Grosskinesthesia, eye movements, and blinks
| Tonic muscle contraction | Tonic muscle contraction
| Other | Other
| 60-Hz electrical Electromechanical device (e.g., ventilators, IV drips) | 60-Hz electrical Electromechanical device (e.g., ventilators, IV drips)

Sleep States

- Quiet sleep = NREM sleep, Active sleep = REM sleep in the adult
- Quiet sleep – little eye movements and increased chin EMG activity with regular respirations and ECG
- NREM: often enters active sleep at onset of sleep
  - Continuous EEG with little eye movements, irregular respirations and cardiac rate; decreased chin EMG activity
  - Suppression of amplitudes of delta, theta, and alpha
  - By term, two patterns of REM
    - First REM cycle, the background is continuous, mixed frequencies in the delta, theta, and alpha range with a partiality of faster frequencies
    - Second REM cycle, which occurs after a period of NREM sleep, the background is more continuous, voltage is lower (20-50 mV), and eye movements are faster

<table>
<thead>
<tr>
<th>Physiological Measure</th>
<th>Awake</th>
<th>Awake/Sleep State</th>
<th>Silent Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMG (Chin)</td>
<td>Phase and tonic</td>
<td>Phase</td>
<td>Tonic</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Irregular</td>
<td>Irregular</td>
<td>Regular</td>
</tr>
<tr>
<td>Eye Movements</td>
<td>Random or pursuits</td>
<td>Rapid eye movements</td>
<td>Absent</td>
</tr>
<tr>
<td>Body Movements</td>
<td>Facial, limbs and body</td>
<td>Sticking and irregular limb movements</td>
<td>None</td>
</tr>
</tbody>
</table>
Sleep States

- healthy controls and with good observations much of sleep is transitional

Delta Brushes

- 26 weeks CA
- Analogous to K complexes in the adult
  - typically occur asynchronously
- Medium- to high-voltage delta intermixed with low- to medium-voltage fast
  - 18- to 22-Hz max centrally
- Prominent feature
  - active sleep by 29-33 weeks
  - quiet sleep 33-38 weeks

Sleep Maturation

Pre-term

- < 28-30 weeks CA record is discontinuous tracé discontinu
- 28-30 weeks CA, some sleep-state differentiation occurs
  - active sleep more continuous than quiet sleep
- Sleep-state differentiation may be difficult until 32-34 wks
- With maturity, the interburst durations decrease, and the amplitude and morphologies of the interburst activity change
- 34-35 weeks CA, other physiological features become increasingly helpful in determining sleep state.

Term

- Tracé alternant (36-38 wks)
  - discontinuous pattern of NREM sleep
    - bursts vs. slow activity (1-4 Hz) alternate with random faster transients at 50-200 mV/s
    - 4-6 seconds and last 2-4 seconds
  - interburst —low-voltage (50-50 mV/s) continuous, somewhat rhythmic activity (theta)
  - infant often has a SWD of NREM state
    - prominent delta delir with some theta rhythms
    - brief periods as early as 35 wks
    - amount of SWD gradually increases 44-46 wks when it almost completely replaces the TA pattern
Timing of EEG Examination

- Timing may have substantial impact on interpretation
- Substantial “nonspecific” normalization may occur after the peak of illness
- Follow up studies are critical
  - After acute illness
  - Important in prematurity to assess maturation

Feature Extraction

- Performed for each state
- Features to be identified include
  - Amplitude
  - Continuity of background activity
  - Frequency
  - Symmetry
  - Reactivity
  - Synchrony
  - Maturational and paroxysmal patterns.

Amplitude

- Electrocerebral inactivity
  - Grave prognosis
    - If not due to postictal state, hypothermia, acute hypoxia, or drug intoxication
    - Majority of infants die or have severe neurological sequelae
  - Benign low-amplitude activity
    - During discontinuous sleep
    - Caput succedaneum, scalp edema, subdural effusions/hematomas

- Low-voltage undifferentiated pattern with background of 5-15 mVs in all states
  - Associated with poor outcomes
  - Observed in a variety of neonatal encephalopathies
  - Less concerning in acute hypoxia

Continuity

- One of the most striking features of the neonatal EEG is discontinuity
- Vary significantly to their CA and state
- No absolute criteria currently exist to determine excessively discontinuous
  - Hahn et al. (IBIs)
  - Conservatively stated, the maximum IBI duration should be less than 40 seconds in infants younger than 30 weeks CA; by term, the IBIs should be less than 6 seconds in duration.
Continuity

- The most obvious abnormality of continuity is burst-suppression
  - bursts of high-voltage (1-10 s) → marked attenuation (<5 mVs)
  - bursts (highly synchronous between hemispheres) contain no age-appropriate activity and is invariant minimally altered by stimuli, and persistent
- Difficulty in PT (<34 wks) owing to discontinuous periods of nearly absent activities between bursts
- Testing for reactivity
- In young PT infants, serial recordings are advisable

Frequency

- Records that are excessively slow or fast are unusual in neonates
- Rarely, a neonatal record consists of diffuse delta activity in both waking and sleep states, minimal theta or faster frequencies, and poor reactivity
- When these conditions persist longer than 2 weeks in FT neonates, the prognosis is poor.

Symmetry

- **Amplitude and waveform composition**
  - No universal agreement for amplitude
  - Guideline - abnormal if amplitude difference exceeds 2:1
  - Transient interhemispheric asymmetry is likely a normal variant

Synchrony

- CNS maturation in the developing neonate
- **Asynchrony** – bursts of morphological similar activity, homologous head region separated by more than 1.5-2.0 s
- **Assessed during TA and NREM sleep**
- Hypersynchrony < 30 weeks
  - Pathophysiology unknown
- > 30 weeks asynchronous bursts
  - 31-32 wks 70% synchronous
  - 33-34 wks 80% synchronous
  - 35-36 wks 85% synchronous
  - > 37 wks 100% synchronous
Maturation

- From PT to FT and beyond occurs in a predictable time-linked fashion
  - Related to anatomical and functional changes
    - Anatomic appearance
    - Synaptic connectivity
    - Time-dependent genetic expression of neurotransmitter receptor subunits
- EEG a valuable tool in assessing central nervous system physiological maturation

EEG Ontogeny

- **24-20 weeks**
  - Discontinuous
  - Brief periods of moderate-amplitude activity
    - Delta brushes
    - Burst of rhythmic occipital and temporal theta
  - BI 6-12 s
  - Although infant clinically cycles through awake/sleep, little difference in EEG
    - No definite state organization

EEG Ontogeny

- **30-32 weeks**
  - First appears some distinguishing features of wake/sleep
  - Wake and active sleep relatively more continuous – with longer BI’s
  - Bursts still occipital delta with brushes
  - Burst of rhythmic theta are more temporal than occipital
  - BI 5-8 seconds
    - *Tracé discontinu*
  - Some reactivity to external stimulation

EEG Ontogeny

- **33-34 weeks**
  - Active and quiet sleep are more clearly distinguishable
  - Less of the EEG is indeterminate
  - In awake and sleep EEG is more continuous
  - Occipital delta fading and more rhythmic temporal theta
  - Delta brushes more common in quiet sleep (prior to this age more in awake/active sleep)
  - BI’s 5-8 seconds
EEG Ontogeny

- **35-36 weeks**
  - Behavioral states easily distinguishable
  - Definite and reproducible reactivity to external stimulation
  - Continuous in wakefulness in active sleep
  - Admixed frequencies from delta to beta
  - Few delta brushes
  - Quiet sleep remains discontinuous
  - IBI’s 4-6 s — tracé alternant
  - Delta brushes more abundant in quiet sleep

- **37-40 weeks**
  - Clearly recognizable states
  - Tracé alternant — IBI’s 2-4 s, all bursts are synchronous
  - If sleep persists continuous moderate to high amplitude delta activity — CSWS
  - Delta brushes in quiet sleep

- **41-44 weeks**
  - Delta brushes disappear by 44 weeks
  - Moderate to low amplitude mixed frequencies
  - Occasional biphasic lambda waves
  - CSWS replaces Tracé alternant except quiet sleep
  - IBI’s 2-4 s

- **45-46 weeks**
  - Appearance of spindles in CSWS
    - Not well synchronized
    - 12-14 Hz
EEG Ontogeny

• 40-42 wks
  – no delta brushes
  – complete interhemispheric synchrony between bursts of TA is observed
  – infant should cycle through clear sleep states
• 44 wks continuous slow-wave pattern should be predominant during NREM sleep
• 48 wks
  – TA should be minimal
  – NREM sleep dominated by high-voltage slow-wave activity
  – Some sleep spindles also should emerge

CR 1 d old male, FT infant

• Transferred in to NICU at 5 hours for ?seizures
• Recurrent periods of apnea with R eye deviation and sucking/chewing movement
• Normal pregnancy, term delivery
• ROM x 35 hours. Prolonged 2nd stage of 3.5 hours. Were prepping for C/S when mom delivered.
• Babe flat at birth and required bag and mask ventilation for 5 minutes. Following that, floppy and not interested in feeding

Neonatal seizures

• Is it a seizure? Need to consider other phenomena (jitteriness, posturing, sleep myoclonus)
• frequently partial rather than generalized
• usually reflect serious underlying neurologic disease

Etiologies to consider

• Hypoxic-ischemic injury – 2/3 of cases
• Infection (meningitis, encephalitis)
• Vascular (intracranial hemorrhage, infarction, venous thrombosis)
• Metabolic (transient metabolic, inborn errors of metabolism)
  – Pyridoxine dependent seizures
• Cerebral malformation
• Idiopathic
• Familial
Clinical classification of neonatal seizures

- **Clonic (25%)**
  - Focal (unifocal, multifocal)
  - Hemiconvulsive
  - Axial

- **Tonic (20%)**
  - Focal (limb, asymmetric truncal posturing, eye deviation)
  - Generalized

- **Myoclonic (25%)**
  - Focal
  - Generalized (commonly no EEG)

- **Motor automatisms**
  - Oral-buccal-lingual
  - Ocular (excluding tonic deviation)
  - Movements of progression (swimming, bicycling)

- **Other uncommon manifestations**
  - Cessation of motor activity
  - Infantile spasms
  - Apnea (rarely a seizure when occurring alone)

Diagnostic workup of neonatal seizures

- Serum glucose, calcium, magnesium, ammonia, lactate, pH, and a complete chemistry panel
- Cerebrospinal fluid
- Cranial ultrasound
- EEG with infusion of pyridoxine
- Toxicology screen
- Urine organic acids, serum and cerebrospinal fluid amino acids
- Maternal and fetal titers for congenital infection
- CT scan (hemorrhage and calcium) or MRI scan (cerebral malformation, ischemia)

Treatment

- Treat underlying cause
- Phenobarb (Loading 20 mg/kg IV, further boluses of 5-10 mg/kg to total dose of 40 mg/kg. Maintenance 5mg/kg/24h)
- Midazolam
- Phenytoin (Loading 20 mg/kg. Maintenance 5mg/kg/24h)
- If due to HIE, can usually stop AEDs after 48-72 hours

Neonatal seizures: long-term outcome

- High mortality (30%) and morbidity (50%) of survivors
- Approximately 30% of survivors develop epilepsy
- Worst outcome in infants with hypoxic-ischemic encephalopathy, meningitis, and cerebral malformations
- Better outcome with transient neonatal hypocalcemia, idiopathic and familial seizures, and stroke
- Neonatal EEG, neurologic examination, and imaging results are best predictors of outcome
Benign Familial Neonatal Convulsions

- Autosomal dominant (85% penetrance)
- Seizures begin 3rd day of life
- Clonic, tonic and partial often with automatisms
- Neurologically normal
- Most have spontaneous remission
  - 10-15% will have subsequent epilepsy usually generalized - generalized seizures
- K+ channel gene (chromosomes 20 and 8)

Early Myoclonic Encephalopathy (EME)

- Very early onset (<28 days) – often first hours
- Ictal phenomena
  - Partial or fragmentary erratic myoclonus
    - Face and limbs
  - Partial motor seizure
  - Sometimes massive myoclonus
  - Late occurrence of massive myoclonus
- EEG shows suppression burst pattern
- Usually cryptogenic, metabolic non ketotic hyperglycenemia

EME

- Treatment
  - Resistant to anti-convulsants and ACTH
- Prognosis
  - Neurological development remains absent or rudimentary
  - Death in about 50% in first year of life
Conclusions

• Often technically difficult with challenges in interpretation
• Provides useful information that reflects function of neonatal brain
• Useful in assessing prognosis for neurologic sequelae