EEG Developmental Maturation, Neonatal seizures and Neonatal Encephalopathies

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• Nothing to disclose
Objectives

• 1. Describe the process of EEG maturation in preterm and term babies
• 2. Discuss the epidemiology, etiology and evaluation of neonatal seizures.
• 3. Describe the clinical and EEG characteristics and treatment of the neonatal seizures
• 4. Update the diagnosis and electroclinical characteristics of neonatal encephalopathy
EEG DEVELOPMENTAL MATURATION
Definitions

- Neonate: Newborn infant less than 4 weeks of age
- Preterm: Conceptional age usually 24 to <34 weeks
- Near term: Conceptional age 34 to <37 weeks
- Term: Conceptional age 37 weeks and above
Embryogenesis

Basic Organization of the Neonatal EEG Background

- Continuity and discontinuity
- Symmetry
- Synchrony
- Amplitude
- Reactivity
- Specific composition of the background or grapho-elements
# Neonatal EEG Background Evolution in different behavioral states

<table>
<thead>
<tr>
<th>Conceptional age</th>
<th>Awake (eyes open)</th>
<th>Active Sleep (eyes closed)</th>
<th>Quiet Sleep (eyes closed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-29 weeks</td>
<td>![Waveform]</td>
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<td>30-34 weeks</td>
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<td>35-36 weeks</td>
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<td>![Waveform] TA</td>
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<tr>
<td>37-40 weeks</td>
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<td>![Waveform]</td>
<td>TA &amp; CSWS</td>
</tr>
<tr>
<td>40-44 weeks</td>
<td></td>
<td>![Waveform]</td>
<td>CSWS</td>
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<tr>
<td>44-46 weeks</td>
<td></td>
<td>![Waveform]</td>
<td>CSWS &amp; spindle</td>
</tr>
</tbody>
</table>

Modified from Fig 6.23. Ebersole JS & Pedley TA Current Practice of Clinical Electroencephalography. 3rd edition. 2003
Continuity

Continuous EEG
Refers to relatively steady amplitude

Discontinuous EEG
Refers to “on periods” (BURST) and “off periods” (INTERBURSTS)

Interburst interval (IBI): discontinuation portion of the EEG
25 day old baby girl born at 39 weeks GA

Trace Alternant

Quiet Sleep
Continuous EEG
Basic Organization of the Neonatal EEG Background

- **Amplitude**
  - Measured in voltage
  - Voltage: peak to peak value
  - Amplitude of the graphoelements decreased from 24 wks CA to term
Basic Organization of the Neonatal EEG

Background

• Symmetry
  – Amplitude, frequency and waveform elements of the neonatal EEG should be SYMMETRIC
Asymmetric BG
Basic Organization of the Neonatal EEG Background

• Synchrony
  – bursts and graphoelements are synchronized if there is < 1.5 seconds separating the onset of the bursts between the right and left hemisphere

  – Normal synchrony
    • < 29 wks CA: 100%
    • 31-36 wks CA: 70%
    • >37 wks CA: 100%
Asynchrony example
Basic Organization of the Neonatal EEG

Background

• Reactivity: Clinical and/or EEG response to external stimulation or internal arousal

• Clinical response:
  – Active movements
  – Respiratory pattern changes

• EEG response:
  – Frequency changes
  – Increased continuity
  – Decreased amplitude
  – Change from sleep to awake pattern

Photic stimulation does not produce photic driving in the term neonate
Basic Organization of the Neonatal EEG

Graphoelements

- Monomorphic occipital delta
- Delta brushes
- Rhythmic temporal theta
- Anterior dysrhythmia
- Encouches frontales

- 24-34 weeks
- 24-36 weeks, peak 34 weeks, sometimes seen at term during quiet sleep
- 24-34 weeks
- 35-44 weeks
- 34-44 weeks
Central delta brushes, right temporo-occipital theta

32 weeks CA, sleep
25 day old baby girl born at 39 weeks GA

Anterior frontal dysrhythmia

Encouches frontales

Quiet Sleep
The American Clinical Neurophysiology Society’s Guideline on Continuous Electroencephalography Monitoring in Neonates

Renée A. Shellhaas,* Taeun Chang,† Tammy Tsuchida,† Mark S. Scher,‡ James J. Riviello,§ Nicholas S. Abend,¶ Sylvie Nguyen,‖ Courtney J. Wusthoff,‖ and Robert R. Clancy‖

Key Words: Electroencephalography, EEG, Amplitude-integrated EEG, Intensive care, Neonatal seizures, Hypoxic ischemic encephalopathy.

(J Clin Neurophysiol 2011;28: 611–617)

et al., 2000; Wyatt et al., 2007), and are potentially treatable by the administration of antiseizure medications (Painter et al., 1999; Rennie and Boylan, 2007; Silverstein and Ferriero, 2008), the largest role of EEG monitoring is the surveillance for and prompt treatment
Who needs continuous EEG?

• Neonates with severe asphyxia and/or on cooling protocol
• Neonates with strong suspicion for seizures (recurrent rhythmic body movements or unexplained apneas)
• Neonates with encephalopathy
• Critically ill neonates on ventilator or with neuromuscular blocking agents
  – Pre and post cardiac surgery
• Neonates with moderate to severe abnormalities on routine EEG
NEONATAL SEIZURES
Epidemiology

• Neonatal seizures occur in 1.5–3.5 per 1000 live term births (Eriksson and Zetterstrom, 1979; Lanska et al., 1995; Ronen et al., 1999).

• 2006-2012 in USA, prevalence of neonatal seizures is 0.04%. (Padiyar S et al 2020)
  – Highest prevalence at 24 week GA = 0.12%

• Mortality rate in infants with seizures is 4%
  – Higher prevalence between 33-36 weeks GA
Epidemiology
Etiology does matters!

• Neonatal seizures occur in up to 26% of neonates with HIE (Shellhaas et al. 2011; Tsuchida et al. 2013; Massaro et al. 2015)

• Electrographic neonatal seizures is seen in 11.5% of neonates undergoing heart surgery (Clancy RR et al. 2005)
Epidemiology

• The incidence of neonatal seizures is:
  – higher rates in preterm neonates
  – increased with decreasing gestational age and
  – Increased with decreasing birth weight
    • ≥2500 g:1.19/1000,
    • <1000 g: 127.57/1000)

(Pisani F eta l. 2017)
Etiology of Neonatal Seizures

- Hypoxia Ischemic Encephalopathy
- Intraventricular Hemorrhage
- Stroke
- Metabolic disorders and transient alteration of Glycemic and electrolytes
  - Hypoglycemia
  - hypo or hypernatremia
  - hypocalcemia
- CNS infections and sepsis
- Trauma
- Intoxication

- Genetic causes
  - Malformations of cortical development
    - Neuronal Migration Disorder
    - Polymicrogyria (e.g. TUBA1A)
    - Pachygyria-lissencephaly spectrum 9e.g. LIS1, ARX
    - Overgrown spectrum
    - Hemimegalencephaly (e.g. PIK3CA)
    - Focal cortical dysplasia (e.g. DEPDC5)
    - Tuberous Sclerosis complex (TSC1, TSC2)
    - Microcephaly (e.g. PNKP, CASK)
  - Genetic Cellular
    - Genetic syndromes
    - Chromosomal disorders
    - Neurocutaneous syndrome
    - Pseudo-TORCH Syndromes
    - Channelopathies
    - Synaptic vesicle docking and release
    - Cell signaling
    - Vascular Malformations of genetic etiology
      - COL4A1-related poroencephaly, schizencephaly or prenatal hemorrhage or prenatal hemorrhage
      - Vascular malformations with genetic etiology (cavernous malformations, AVMs)
    - Genetic risk factors for genetic stroke
    - Genetic metabolic or inborn error of the metabolism
Fig. 2. Diagnostic approach to neonatal seizures. EEG, electroencephalogram; 3 T magnetic resonance imaging; MRS, magnetic resonance spectroscopy; CSF, cerebrospinal fluid; 5-MTHFR, methylenetetrahydrofolate reductase; LP, lumbar puncture; 5P5, pyridoxal-5′-phosphate; AA, amino acid; VLCFA, very long chain fatty acid.

Olson H et al.
Contemporary Profile of Seizures in Neonates: A Prospective Cohort Study

Hannah C. Glass, MDCM, MAS1,2, Renée A. Shellhaas, MD, MS3, Courtney J. Wusthoff, MD4, Taeun Chang, MD5, Nicholas S. Abend, MD6, Catherine J. Chu, MD7, M. Roberta Cilio, MD, PhD1, David V. Glidden, PhD2, Sonia L. Bonifacio, MD, MAS8, Shavonne Massey, MD6, Tammy N. Tsuchida, MD, PhD5, Faye S. Silverstein, MD3, and Janet S. Soul, MDCM9, on behalf of the Neonatal Seizure Registry Study Group*

Objective To determine the incidence of seizures in neonates monitored with continuous EEG, and to assess their incidence, timing, and outcome.

Study design We conducted a prospective cohort study of neonates born at 44 weeks’ gestation or who had other high-risk conditions and who were discharged alive. The time at risk for seizures was defined as the period from birth to discharge. The primary outcome was the occurrence of a first seizure, defined as an electroencephalogram (EEG) abnormality or clinical seizure requiring medication. The secondary outcomes were the number of seizures, the duration of seizures, and the occurrence of status epilepticus.

Results The most common etiology for seizures in neonates was hypoxic ischemic encephalopathy (38%), followed by ischemic stroke (18%) and intracranial hemorrhage (11%). Status epilepticus occurred in 12% of cases, and 52% of infants received ≥2 antiseizure medications. During the neonatal admission, 17% died; 49% of survivors had abnormal neurologic examination at hospital discharge. In an adjusted analysis, high seizure burden was associated with increased mortality and morbidity.

Conclusions In this large contemporary cohort of consecutively enrolled newborns with seizures treated at centers that use cEEG per the guidelines of the American Clinical Neurophysiology Society, about one-half had high seizure burden, received ≥2 antiseizure medications, and/or died or had abnormal examination at discharge. Greater seizure burden was associated with increased morbidity and mortality. These findings underscore the importance of accurate determination of neonatal seizure frequency and etiology and a potential for improved outcome if seizure burden is reduced. (J Pediatr 2016;174:98-103).
Definition of neonatal seizures

• Electrographic and Electro-Clinical Seizures
Neonatal seizures

Figure 1  Total recorded electrographic seizure activity measured in seconds, versus total clinical seizure manifestations in nine patients with electrographic seizures recorded on continuous video-EEG during the first 72 hours of life.

Neonatal EEG seizures

- Sudden
- Repetitive
- Evolving
- Clear onset, middle and end
- Stereotyped ictal pattern
- Amplitude at least 2μV
Common patterns for neonatal seizures

1-2 Hz seizure pattern

Fast frequency seizure pattern
Neonatal EEG seizures
Electrographic characteristics

• Neonates have a high seizure burden (~7 seizures per hour)
• Often seizures are surface positive
• Minimal duration of the seizures is 10 seconds
  – Mean duration of seizures is around 90 seconds
  – Minimal duration between 2 seizure patterns has to be ≥10 seconds to be consider independent seizures
• Background pattern can be present during the seizure and often is abnormal
Seizure burden in neonates

Out of 21 neonates, 14 had more than 10 szs in 48 hours

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Objective To determine the contemporary etiology, burden, and short term outcomes of seizures in neonates monitored with continuous vide

Study design We prospectively assessed between January 2013 and March 2014 American Clinical Neurophysiology and outcome were determined.

Results The most common seizure types were status epilepticus (16%), intracranial hemorrhage (8%), ischemic stroke (18%), and seizures (56% male, 88% term) were associated with increased morbidity and mortality. These findings underscore the importance of accurate determination of neonatal seizure frequency and etiology and a potential for improved outcomes if seizure burden is reduced. (J Pediatr 2016;174:98-103).

- Seizure burden
  - => 7 EEG seizures/hour 59%
  - Status epilepticus 16%
  - Survivors (56% male, 88% term) were at study onset.
  - Survivors had abnormal neurologic examination at hospital discharge. In an adjusted analysis, high seizure burden was a significant risk factor for mortality, length of hospital stay, and abnormal neurological examination at discharge.

Conclusions In this large contemporary cohort of consecutively enrolled newborns with seizures treated at centers that use cEEG per the guidelines of the American Clinical Neurophysiology Society, about one-half had high seizure burden, received ≥2 antiseizure medications, and/or died or had abnormal examination at discharge. Greater seizure burden was associated with increased morbidity and mortality. These findings underscore the importance of accurate determination of neonatal seizure frequency and etiology and a potential for improved outcomes if seizure burden is reduced. (J Pediatr 2016;174:98-103).
Seizures can involve a single electrode

Often the seizures are multifocal

Often the seizures are simultaneous multifocal
C3 seizure, no clinical signs

78% of neonatal seizures appeared in the C3 → C4 channel.
Sz with independent rhythms
Clinical symptoms

- Subtle seizures (50%)
  - Ocular movements
  - Oro-buccal-lingual movements
  - Progression movements (pedaling, bicycling, etc)
  - Autonomic symptoms
  - Complex purposeless movements (arousals, crying, hyperactivity)

- Tonic seizures (5%)  
- Clonic seizures (25%)  
- Myoclonic seizures (20%)  
- Non-paroxysmal repetitive behaviors  
- Spasms

Volpe Mizhari
Sequential Seizures:
(ILAE Neonatal Task Force and the 2017 ILAE classification manual)
-difficult to identify the dominant feature,
-typically in longer seizures
-sequence of clinical features was seen, often with changing lateralization
Neonatal seizures: location
Premature versus Term babies

Fig. 2. Localisation of seizure onset. (A) Onset of focal seizures was observed in all cerebral regions and on the whole, the central regions predominated. (B) We observed differences depending on age. In the youngest neonates, the onset over posterior regions predominated, whereas frontal onset was observed only after 28 weeks CA.

S. Janác̆ková et al. / Clinical Neurophysiology 127 (2016) 2721–2727
## Relation between etiology and seizure types in neonates

<table>
<thead>
<tr>
<th>ETIOLOGY</th>
<th>Hypoxia-Ischemic Encephalopathy</th>
<th>Vascular</th>
<th>Genetic</th>
<th>Metabolic/Electrolytes</th>
<th>Inborn Error of the Metabolism</th>
<th>Infection</th>
<th>Cortical Malformation</th>
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</thead>
<tbody>
<tr>
<td><strong>SEIZURE TYPES</strong></td>
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<td>EEG seizures</td>
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<td>Clonic seizures</td>
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<td>Tonic seizures</td>
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<tr>
<td>Myoclonic seizures</td>
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<td>Autonomic seizures</td>
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<td>Spasms</td>
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</tbody>
</table>

### Critical Review and Invited Commentary

**Neonatal seizures: Is there a relationship between ictal electroclinical features and etiology? A critical appraisal based on a systematic literature review**

*Magda L. Nunes¹ | Elissa G. Yozawitz² | Sameer Zuberti³ | Eli M. Mizrahi⁴ | Maria Roberta Cilio⁵ | Solomon I. Moshé⁶ | Perrine Plouin⁷ | Sampsa Vanhatalo⁸ | Ronit M. Pressler⁹ | Task Force on Neonatal Seizures, ILAE Commission on Classification & Terminology*
Neonatal Status Epilepticus

• Single seizure lasting more than 30 minutes

• Multiple seizures that account for 30 minutes over one hour period

• Recurrent seizures for over 50% of 1-3 hours of recording time (Nash KB et al. Neurology 2011; 76: 556-62)
Table 2
Quantitative seizure characteristics and comparisons between conventional and single channel EEG

<table>
<thead>
<tr>
<th></th>
<th>Conventional EEG</th>
<th>C₃ → C₄</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures detected</td>
<td>N = 851</td>
<td>N = 664 (78%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean seizure duration (s)</td>
<td>132 (10–2314)</td>
<td>100 (10–2313)</td>
<td>( p \leq 0.001^b)</td>
</tr>
<tr>
<td>Mean ictal peak-to-peak amplitude ((\mu)V)</td>
<td>145 (13–1166)</td>
<td>111 (5–739)</td>
<td>( p \leq 0.001^b)</td>
</tr>
<tr>
<td>Mean ratio of ictal to interictal peak-to-peak amplitude ((\mu)V)</td>
<td>2.19 (0.5–27.1)</td>
<td>2.27 (0.4–33.8)</td>
<td>( p = 0.47^b)</td>
</tr>
<tr>
<td>Mean seizure burden (percent record with seizure)</td>
<td>24.8% (0.7–86.9)</td>
<td>17.6% (0–18.0)</td>
<td>( p = 0.004^b)</td>
</tr>
<tr>
<td>Mean seizures per hour</td>
<td>7.0% (0.5–21)</td>
<td>5.2 (0–18)</td>
<td>( p = 0.003^b)</td>
</tr>
<tr>
<td>Status epilepticus(^d)</td>
<td>17/125 (14%)</td>
<td>7/125 (6%)</td>
<td>( p = 0.038^a)</td>
</tr>
</tbody>
</table>

\(^a\) Chi-squared.
\(^b\) Student’s \(t\)-test.
\(^c\) There is only a moderate correlation (Spearman coefficient = 0.58) between the number of seizures per hour and the seizure burden.
\(^d\) Status epilepticus was defined as greater than 50% of the tracing with seizures.
Pathophysiology

Fig. Schematic depiction of maturational changes in glutamate and GABA receptor expression and function in the developing brain. Developmental pattern for rat (top x-axis) and human (bottom x-axis) are shown, based on recent literature. GABA receptors are depolarizing (light blue line) early in the first postnatal week in the rat and up to and including the neonatal period in the human, whereas functional inhibition (black line) is gradually reached over development. Before full maturation of GABA-mediated inhibition, the N-methyl-D-aspartate (NMDA; dark blue line) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA; orange line) subtypes of glutamate receptors peak between the first and second postnatal weeks in the rat and in the neonatal period in the human. Kainate receptor binding (green line) is initially low and gradually increases to adult levels by the fourth postnatal week.
Treatment

• First line
  – phenobarbital (doses ranging from 20–40 mg/kg),
  – phenytoin (20 mg/kg), or fosphenytoin, and/or
• Second-line adjuvant (first line in some centers)
  – benzodiazepines such as lorazepam (0.05–0.1 mg/kg)
  – midazolam
• Other:
  – Lidocaine (77% response versus Midazolam 50% for HIE)
  – Topiramate
  – Levetiracetam
  – Bumetanide 0.3mg/kg -> concern for hearing loss (Pressler RM et al. 2015)

HIE = hypothermia

Table III. Seizure management among 426 neonates with clinically suspected and/or EEG confirmed seizures who were monitored by cEEG

<table>
<thead>
<tr>
<th>Overall, n = 426</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial loading medication and dose</td>
</tr>
<tr>
<td>Phenobarbital (20 mg/kg, IQR 20, 20 mg/kg)</td>
</tr>
<tr>
<td>Levetiracetam (20 mg/kg, IQR 20, 32 mg/kg)</td>
</tr>
<tr>
<td>Fosphenytoin (20 m/kg, IQR 15, 20 mg/kg)</td>
</tr>
<tr>
<td>No loading dose</td>
</tr>
<tr>
<td>Seizure medications administered during the admission</td>
</tr>
<tr>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Fosphenytoin</td>
</tr>
<tr>
<td>Benzodiazepine – intermittent doses</td>
</tr>
<tr>
<td>Benzodiazepine infusion</td>
</tr>
<tr>
<td>Topiramate</td>
</tr>
<tr>
<td>Carbamazepine/oxcarbazepine</td>
</tr>
<tr>
<td>Vitamin(s): (pyridoxine, folic acid, pyridoxal 5 phosphate)</td>
</tr>
<tr>
<td>Number of antiseizure medications administered</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>≥4</td>
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</table>

Treatment => 2 or more AED 52%

Glass HC et al. 2016
NEONATAL ENCEPHALOPATHY
Neonatal encephalopathy
Clinical manifestations

• Alter mental status
• Seizures
• Hypotonia
• Abnormal primitive reflexes
• Apneas and difficulty breathing
• Feeding problems
• Abnormal cry
Etiology

- Hypoxia Ischemia
- Intracranial infection
- Ischemic perinatal stroke
- Intracranial hemorrhage
- Brain malformations
- Inborn Error of the Metabolism
- Neonatal Onset Epileptic Encephalopathy
  - KCNQ2, KCNQ3, SCN1A, SCN2A, SLC12A5, STXBP1, KCNT2, GDLC, CDKL5, CHD7
- Transient encephalopathy
Neonatal Onset Epileptic Encephalopathy

- Ohtahara syndrome or Early Infantile Epileptic Encephalopathy (EIEE) and Early Myoclonic Epileptic Encephalopathy (EME)

- KCNQ-related epilepsy
  - Benign familial neonatal seizures (BFNS)
  - Benign familial neonatal-infantile seizures (BFNIS)
  - KCNQ severe encephalopathy
Neonatal Onset Epileptic Encephalopathy (Cont.)

- SCN2A-related neonatal epilepsies
- CDKL5 encephalopathy
- STXBP1 encephalopathy
- Other genetic early onset developmental and epileptic encephalopathies
Neonatal encephalopathy with Burst suppression pattern
Clinical features

<table>
<thead>
<tr>
<th>Ohtahara or EIEE with BS</th>
<th>Early Myoclonic Epileptic Encephalopathy (EMEE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tonic seizures</td>
<td>• Myoclonic seizures</td>
</tr>
<tr>
<td>• Onset in the first week of life</td>
<td>• Onset in the first week of life or prenatal</td>
</tr>
<tr>
<td>• Grossly abnormal brain MRI</td>
<td>• Normal brain MRI</td>
</tr>
</tbody>
</table>
Etiology

• Brain structural abnormalities
  – hemimegalencephaly, magalencephaly, lissencephaly, polymicrogyria, focal or multifocal cortical dysplasia, poroencephaly, agenesis of the corpus callosum or the mamillary bodies, posterior fossa abnormalities, etc
  – HIE

• Genetic metabolic
  – ARX, CDKL5, SLC25A22 and STXBP1, KCNQ2, SCN2A and ALDH7A1; mitochondrial diseases, inborn error of the metabolism such as non-ketotic hyperglycinemia or glycine encephalopathy, propioic or methylmalonic acidemia, molybdenum cofactor deficiency, and other more rare inborn errors of the metabolism
## Treatment

<table>
<thead>
<tr>
<th>Neonatal Epileptic Encephalopathy</th>
<th>treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohtahara and EMEE</td>
<td>Topiramate, other AED, Steroids, pyridoxine (Evidence Class C, poorly effective, weak recommendation)</td>
</tr>
<tr>
<td>KCNQ2 - EE</td>
<td>carbamazepine, oxcarbazepine, phenytoin</td>
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<tr>
<td>SCN2A - EE</td>
<td>carbamazepine, phenytoin</td>
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<tr>
<td>CDKL5 - EE</td>
<td>???</td>
</tr>
<tr>
<td>KCNT1 - EE</td>
<td>bromides, levetiracetam, quinidine ???</td>
</tr>
<tr>
<td>STXBP1 - EE</td>
<td>???</td>
</tr>
</tbody>
</table>
QUESTIONS