Epileptic syndrome in Neonates and Infants

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AGE SPECIFIC INCIDENCE OF EPILEPSY

NEONATAL SEIZURES

• Seizures occurring in the first 4 weeks of life
• Most (80%) neonatal seizures occur in the first 1–2 days to the first week of life
• Incidence: 1.5 – 3.5 /1000 live births
• Very high incidence in preterm infants (57–132 per 1000 live births)
COMMON CAUSES OF NEONATAL SEIZURES

- Hypoxic-Ischemic Encephalopathy (most common cause)
- Intracranial hemorrhage, cerebral infarction
- CNS infections (acute or congenital)
- Metabolic (Hypoglycemia, Hypocalcemia, hypomagnesemia, Hypo/hypernatremia)
- Inborn errors of metabolism (NKH, organic acidurias etc.)
- Maternal drug withdrawal
- Neonatal epileptic syndromes
  - Benign Familial Convulsions
  - Benign Neonatal Convulsions (fifth day fits)
  - EIEE (Ohtahara syndrome)
Classification of Neonatal Seizures

1. Subtle 50%
   (tonic, horizontal deviation of the eyes, eyelid blinking or fluttering, sucking, smacking or other oral–buccal–lingual movements, swimming or pedalling movements and, occasionally, apnoeic spells)

2. Clonic (focal, multifocal) 25%

3. Tonic (focal, generalized) 5%

4. Myoclonic (focal, multifocal, generalized) 20%

5. Non-paroxysmal repetitive behaviors

J. Volpe, Neurology of the Newborn 2008, p.203-237
CHALLENGES IN EVALUATING INFANTS WITH EPILEPSY

- Electro-clinical dissociation and some electro-graphic seizures do not produce clinical symptoms
- No recognisable post-ictal state
- Interictal and ictal EEG may show multifocal or generalized abnormalities even in those with focal epilepsy
- MRI difficult to interpret due to lack of myelination and higher water content of brain
- Decreased cortical activity on PET scans
Epileptic Syndrome

• Defined as “an epileptic state with specific signs and symptoms”

• Categorized by
  – Seizure type(s)
  – Age at the onset
  – EEG
  – Neurologic status
  – Precipitating factors
  – Response to AEDs
  – Natural history
  – Genetic
  – Neuroimaging studies
Electroclinical syndromes arranged by age at onset

Neonatal period
- Benign familial neonatal epilepsy (BFNE)
- Early myoclonic encephalopathy (EME)
- Ohtahara syndrome

Infancy
- Epilepsy of infancy with migrating focal seizures
- West syndrome
- Myoclonic epilepsy in infancy (MEI)
- Benign infantile epilepsy
- Benign familial infantile epilepsy
- Dravet syndrome
- Myoclonic encephalopathy in nonprogressive disorders
Epileptic syndrome in neonates

BNFC: Benign neonatal familial convulsion
BNC: Benign neonatal convulsion
BENIGN NEONATAL FAMILIAL CONVULSION (BNFC)

- Rare, Autosomal Dominant
- **Age of onset**: Seizures occur in well newborns on 2-3 day of life and remit by 6 weeks
- **Seizure type**: Tonic seizure or apnea
  - sometimes with focal components (sliding eyes, motor automatisms) and clonic seizures (asymmetrical/unilateral)
- Favorable outcome
- Seizures may recur in later life in 10%
- Mutation in the potassium channel genes (KCNQ2, KCNQ3) causing alteration of slowly inactivating and non-inactivating M-channel currents

*Nordli DR. Epilepsia 2005;46(Suppl 9):48-56*
Benign Neonatal Convulsions (fifth day fits)

- **Age of onset:** occur around the fifth day of life
- **Seizure types:** clonic (unilateral) which may be accompanied by apnea
  - Status epilepticus (2 hours-2 days)
- **EEG patterns:**
  - Interictal: theta wave activity 4-7 Hz which changes sides
  - Ictal: rhythmic spike-slow waves predominantly in the centrotemporal region
- **Healthy, full term infant**
- **Negative evaluations for etiology**
- **Good prognosis, seizures regress spontaneously**
Benign Neonatal Convulsions (fifth day fits)

Theta pointu alternant pattern in a baby with benign neonatal (non-familiar) seizures

Fp2-C4
C4-O2
O2-T4
T4-Fp2
Fp1-C3
C3-O1
O1-T3
T3-Fp1

50 μV
1 sec
<table>
<thead>
<tr>
<th></th>
<th>BINC (fifth day fits)</th>
<th>BNFC</th>
</tr>
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<tbody>
<tr>
<td>Main seizures</td>
<td>Mostly clonic</td>
<td>Tonic-clonic</td>
</tr>
<tr>
<td>Onset</td>
<td>Fifth day of life</td>
<td>2nd or 3rd day of life</td>
</tr>
<tr>
<td>Duration of seizures</td>
<td>Status epilepticus</td>
<td>Repetitive isolated seizures</td>
</tr>
<tr>
<td>Main causes</td>
<td>Unknown, probable environmental</td>
<td>Familial (Autosomal dominant)</td>
</tr>
<tr>
<td>Subsequent seizures</td>
<td>0.5%</td>
<td>11%</td>
</tr>
<tr>
<td>Psychomotor deficits</td>
<td>Minor</td>
<td>Nil</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td>Localized spikes</td>
<td>Generalised flattening</td>
</tr>
<tr>
<td>Interictal EEG</td>
<td>Theta pointu alternant</td>
<td>Normal or focal abnormalities</td>
</tr>
</tbody>
</table>
EIEE: Early Infantile Epileptic Encephalopathy (Ohtahara syndrome)

EME: Early Myoclonic Encephalopathy
EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY (Ohtahara Syndrome)

- Seizure onset within few weeks after birth (< 3 months):
  - Tonic seizures which may occur in clusters
  - Focal motor seizures
  - Hemiconvulsions
  - Generalized tonic-clonic
- EEG: suppression-burst pattern both in sleep and wake states
- Etiology: Major brain malformations, non-ketotic hyperglycinemia, mitochondrial cytopathy, pyridoxine dependency, CPT deficiency, genetic (ARX, STXB1, SLC2A22)
- 75% progress to West syndrome, 12% to LGS

Beal JC et al. Pediatric Neurology 2012;47:317-23
EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY
(Ohtahara Syndrome)

EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY (Ohtahara Syndrome)

• Poor prognosis for seizures, development
• Some overlap with Early Myoclonic Encephalopathy
• Limited response to conventional AEDs; some benefit with ACTH, Ketogenic Diet
• Treatment of Pyridoxine dependency or Biotinidase deficiency, NKH
• Cortical resection, hemispherectomy in selected cases

Beal JC et al. Pediatric Neurology 2012;47:317-23
Early Myoclonic Encephalopathy (EME)

- Age of onset: during 1 months of life
- Seizure patterns: myoclonic seizures
- Partial seizures (frequent)
- Tonic spasms (occasional)
- EEG: Burst-suppression pattern mainly during sleep
- Intractable to AEDs
- Poor developmental prognosis
Early Myoclonic Encephalopathy (EME)

EEG demonstrates suppression-burst pattern mainly noted during sleep. The burst phase is shorter with irregular longer periods of suppression phase than EIEE.

H. Yamamoto et al. Brain & Development 2011
# Early myoclonic encephalopathy (EME) VS. early infantile epileptic encephalopathy (EIEE)

<table>
<thead>
<tr>
<th></th>
<th>EIEE</th>
<th>EME</th>
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</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Within first three months</td>
<td>Neonatal period</td>
</tr>
<tr>
<td><strong>Characteristic seizure type</strong></td>
<td>Tonic spasm</td>
<td>Erratic or fragmentary myoclonus</td>
</tr>
<tr>
<td><strong>Additional seizure types</strong></td>
<td>Focal motor seizures, Hemiconvulsions, Generalized seizures</td>
<td>Massive myoclonus, Simple partial seizures, Infantile spasms (tonic)</td>
</tr>
<tr>
<td><strong>Background EEG</strong></td>
<td>Bursts- Longer, Interburst- Regular, shorter (Sleep and awake)</td>
<td>Bursts-Shorter, Interburst- Irregular, longer (accentuated by sleep)</td>
</tr>
<tr>
<td><strong>(Suppression-burst pattern)</strong></td>
<td></td>
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<tr>
<td><strong>Etiology</strong></td>
<td>Malformation of cortical development</td>
<td>Genetic and metabolic</td>
</tr>
<tr>
<td><strong>Long-term seizure evolution</strong></td>
<td>West syndrome, Lennox-Gastaut</td>
<td>Persistent regression</td>
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Epileptic syndrome in infants

- Epilepsy in infancy with migrating focal seizures
- West Syndrome
- Myoclonic Epilepsy of Infancy
- Benign Infantile Epilepsy
- Benign Familial Infantile Epilepsy
- Dravet Syndrome (Severe myoclonic epilepsy of infancy, SMEI)
- Myoclonic encephalopathy in nonprogressive disorder
WEST SYNDROME

- Described by West in 1841
- Triad:
  - Seizure: infantile spasm (symmetric, salaam-like contractions of trunk + extension and elevation of arms + tonic extension of legs)
  - Developmental delay (85-90%)
  - Typical EEG: hypsarrhythmia and variants
- Ictal EEG: generalized electrodecremental pattern often preceded by a generalized sharp/slow wave
- Age at onset: early infancy, peak 4-7 mo
- Etiology: various causes (FCD, Tuberous sclerosis, etc.)
- Very difficult to treat seizure
West syndrome
Common Etiologies

• Tuberous Sclerosis (10-30%)
• Perinatal (15-25%)
  – Fetal infections
  – HIE/perinatal brain injury
  – Hypoglycemia
• Brain malformations
• Metabolic abnormalities
• Pyridoxine deficiency

Chromosomal Abnormalities:

• Trisomy 21
• ARX
• TSC1
• TSC2
• RDXP2
• ALDH7A1
• POLG
• CDKL5
• STXBP1
• SCN2A
• FOXG1
• PCDH19
• SLC2A1
• MeCP2
Hypsarrhythmia pattern during wakefulness

Chaotic mixture of asynchronous, high amplitude of slow wave intermixed with multifocal spikes
HYPSARRHYTHMIA PATTERN ALTERED BY NREM SLEEP
Video infantile spasm
Ictal EEG

Medium- to high-voltage, positive slow waves maximal at vertex regions with superimposed low-voltage fast activity (ictal), followed by electrodecremental event
Ictal EEG – electrodecremental pattern
TREATMENT OF INFANTILE SPASMS

• Pyridoxine worth trying – stop if no benefit in 3 days
• Benzodiazepine such as Clonazepam. If spasms are not promptly controlled proceed with:-
• ACTH / Vigabatrin which are the only drugs shown to be effective in clinical trials. Should be started within 3-4 weeks of seizure onset
• Topiramate, Zonisamide have some efficacy
• Valproic acid
• Ketogenic Diet
• Epilepsy Surgery when seizures are uncontrolled and there is a focal/unilateral lesion
BENIGN MYOCLONUS OF EARLY INFANCY

- Age of onset: 4-12 mo
- Myoclonic jerks involving neck and extremities
- May occur singly or in clusters
- Elicited by excitement, fear, anger, frustration
- Resemble Infantile Spasms
- EEG is normal both interictally and during jerks
- Video-EEG useful in excluding West Syndrome which requires prompt diagnosis and treatment
- Development progresses normally
- Myoclonic jerks diminish over time, disappear during second year of life

Myoclonic Epilepsy in Infancy

• Rare idiopathic epilepsy – myoclonic seizures in previously healthy children
• Onset: 6 months- 2 years
• Family history of epilepsy in 1/3 of the patients
• Preceding febrile seizures in 20%
• EEG: Spike, multiple spike-wave complexes
• AEDs: VPA
• Mild cognitive impairment (20-40%)
SEVERE MYOCLONIC EPILEPSY OF INFANCY (SMEI)  
DRAVET SYNDROME

- Onset between 6-15 months, often triggered by fever, illness or immunizations
- Seizures:
  - Generalized or hemiclonic convulsions (including status)
  - Myoclonic
  - Atonic, drop attacks
  - Focal dyscognitive/CPS
  - Non-convulsive status epilepticus
- EEG may be normal initially or show focal spikes -> multifocal or generalized spikes, spike-wave complexes
- Developmental initially normal, then slows
- Imaging normal / shows nonspecific atrophy

Scheffer IE. Diagnosis and long-term course of Dravet syndrome.  
SEVERE MYOCLOWNIC EPILEPSY OF INFANCY (SMEI)  
DRAVET SYNDROME

- Unfavorable outcome due to ongoing seizures, MR
- Course appears to stabilize after age 5 years
- Genetic etiology
  - 70% - 80% have mutations of voltage gated sodium channel gene SCN1A (usually de novo)
  - Girls who are SCN1A negative may have mutations involving PCDH-19 (Protocadherin-19) gene
- Avoid drugs which act via the sodium channel:
  - CBZ, OXC, PHT and LTG

Scheffer IE. Diagnosis and long-term course of Dravet syndrome.  
Table 1. Main characteristics of the epileptic syndromes that present in infancy

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Main Characteristics</th>
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<tbody>
<tr>
<td>Early infantile epileptic encephalopathy</td>
<td>First months; tonic seizures, spasms; suppression-burst; severe outcome</td>
</tr>
<tr>
<td>Early myoclonic epilepsy</td>
<td>First months; myoclonias, spasms; suppression-burst (sleep); severe outcome</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>First year; spasms; hypsarrhythmia; developmental delay</td>
</tr>
<tr>
<td>Dravet syndrome</td>
<td>First year; partial and generalized seizures, myoclonias; normal EEG at onset; later:</td>
</tr>
<tr>
<td></td>
<td>generalized spike-waves and multifocal spikes; severe outcome</td>
</tr>
<tr>
<td>Myoclonic astatic epilepsy</td>
<td>First year; generalized myoclonic and astatic seizures; interictal parietal theta</td>
</tr>
<tr>
<td></td>
<td>activity and bilateral spike-waves; variable outcome</td>
</tr>
<tr>
<td>Malignant migrating partial seizures of infancy</td>
<td>First year; continuous electrographic seizures, multiple areas of onset; severe</td>
</tr>
<tr>
<td>Generalized epilepsy with febrile seizures (+)</td>
<td>outcome</td>
</tr>
<tr>
<td>Hemiconvulsion-hemiplegia-epilepsy</td>
<td>Variable seizure and developmental phenotype in addition to febrile seizures and</td>
</tr>
<tr>
<td></td>
<td>afebrile generalized convulsions</td>
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<tr>
<td>Benign myoclonic epilepsy</td>
<td>Prolonged unilateral febrile seizures; subsequent hemiparesis and partial epilepsy</td>
</tr>
<tr>
<td>Benign familial/nonfamilial seizures</td>
<td>First 3 years; myoclonic seizures; normal interictal EEG; normal development</td>
</tr>
<tr>
<td></td>
<td>First year; partial seizures; normal development</td>
</tr>
</tbody>
</table>

Thank you for your attention