Epileptic Syndromes in Neonates and Infants

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“Age” does matter in young babies

Neonatal period:
the first 28 days of life of a full-term infant (FT)

For preterm infant (PT):
“conceptional age”

Conceptional age = Gestational age + Chronological age

GA: duration of pregnancy
Chronological age: age from the time of birth
Neonatal seizures

- Most vulnerable period of life for developing sz
- Greatest occurrence in the first week
- Incidence 3: 1,000 live births
- Very high incidence in PT 57-132: 1,000
- May be short lived event
- Acute symptomatic >> epilepsy
- Often signify serious malfunction/damage to the immature brain
Etiology of Neonatal Seizures

- Hypoxic-ischemic encephalopathy (FT,PT)
- Cerebral artery/vein infarction
- Hemorrhage
  - Subarachnoid, subdural (FT),
  - Germinal matrix-intraventricular (PT>FT)
- Metabolic:
  - hypoglycemia, ↓Na, ↓Ca, ↓Mg, inborn errors of metabolism
- Infections: TORCH, meningitis, encephalitis
- Major malformations:
  - lissencephaly, pachygyria, polymicrogyria
- Drug withdrawal and toxic
Clinical Manifestations of Neonatal Seizures

• Paroxysmal, repetitive, stereotype

• Usually clinical subtle, inconspicuous and difficult to recognise from the normal behaviors or physiologic phenomena

• No recognisable post-ictal state.

• Frequently be overlooked
Classification of Neonatal Seizures

1. Subtle 50%
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
Subtle Seizures In Neonates

- **Ocular phenomena**
  - Tonic deviation of eyes with/without jerking
  - Sustained eye opening with ocular fixation

- **Oral-buccal-lingual movements**
  - Chewing, sucking, smacking, tongue protrusion

- **Other manifestations**
  - Limb movements: swimming, pedaling, trashing, rowing
  - Autonomic: paroxysmal change in HR, respiration, BP
  - Apnea, hiccup

_J. Volpe, Neurology of the Newborn 2008, p.203-237_
Motor Seizures In Neonates

- Clonic (focal, multifocal) 25%
  Face, limbs, axial muscle
  Hemiconvulsion
- Tonic (focal, multifocal, generalized) 5%
  Generalized (tonic extension)- no EEG correlate
- Myoclonic (focal, multifocal, generalized) 20%
  PT>FT
  Associated with the most severe brain damage
  **Focal motor seizures → high correlation with focal brain lesion

J. Volpe, Neurology of the Newborn 2008, p.203-237
EEG in Neonatal Seizures

• Inter-ictal EEG:
  – sharp/spikes are not reliable marker
  – Suppression-burst pattern: syndrome diagnosis, severe HIE, Preterm, drugs

• Ictal pattern:
  – Highly variable, rhythmic activity
  – Localized to relatively small area
  – Usually focal
  – Multi-focal: independent discharges, differing morphology & frequency
Laplacian Montage

↑ Jerking of left foot
↓ No other apparent clinical manifestations

↑ Mouthing movements

Sneezes
He looks undisturbed and there are no apparent clinical manifestations.
Diagnosis of Neonatal Seizures

• Differentiate between non-epileptic vs epileptic:
  – Suppressed by restrain or repositioning?
  – Elicited by tactile stimulation?
• Detailed Hx of risk/etiology:
  – Pregnancy -> birth -> afterbirth, Family Hx
• Physical exam
  – Altered mental status, AF, focal neuro signs
  – Dysmorphic features, neurocutaneous stigmata
  – Peculiar odours
Diagnosis of Neonatal Seizures

• Screen for common and treatable etiology:
  – Infection: CBC, LP
  – Metabolic: electrolytes, Ca, Mg, lactate, NH3, UA (ketone)
• Consider possible structural brain lesion:
  – Otherwise healthy FT with focal seizure → stroke
  – Inv: USG for bleeding, CT for focal structural lesion eg stroke
• EEG (60 min) may be helpful in Dx of subtle sz, epileptic syndrome and Rx of SE
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 Neonate

• Benign familial neonatal epilepsy (BFNC)
• Early Myoclonic Encephalopathy (EME)
• Ohtahara syndrome (Early Infantile Epileptic Encephalopathy, EIEE)
Epileptic Syndrome in Infancy

- 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
Benign Neonatal Convulsions

Benign Familial Neonatal Seizures (BFNC)

Benign Idiopathic (non-familial) Neonatal Seizures (BINC)
Clinical Case

- A previously healthy male neonate having frequent seizures at age 3 days.
- He had 4-8 sz/day, tonic motor activity, apnea 5-10 sec, vocalization, chewing and occasional focal clonic seizures. He was normal between his fits.
- Normal PE. All tests and interictal EEG were normal.
- Recommended treatment with AED was vigorously rejected by grandmom, who herself, her father and 2 of her 4 children had similar neonatal seizures without any consequences in their successful lives.
Benign Familial Neonatal Convulsions (BFNC)

- Autosomal dominant, 85% penetrance
- Incidence 4.4: 100,000 live births, F=M
- Voltage-gated potassium channel: KCNQ2, KCNQ3
- Seizures in the 2\textsuperscript{nd}-3\textsuperscript{rd} day of life
  - Brief (1-2 min), frequent (20-30/day) seizures
  - Apnea, tonic, generalized clonic
  - Disappear by age 2-6 months
- Favorable outcome, subsequent epilepsy 14%
<table>
<thead>
<tr>
<th></th>
<th>BINC</th>
<th>BFNC</th>
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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>2\textsuperscript{nd} or 3\textsuperscript{rd} 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>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>
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</table>
BINC (Fifth-day fits)

- Occur around the fifth day of life (day 1-7)
- Males > females
- Seizures: clonic (partial) and/or apneic,
- Status epilepticus: 2 hr–3 days (median 20 hr)
- Variable inter-ictal EEG
- Ictal recordings: unilateral or generalized spikes or slow waves
- Diagnosis by exclusion
- Good outcome but increased risk of minor neurological impairment
Early Infantile Epileptic Encephalopathies with Suppression-Burst

**Early Infantile Epileptic Encephalopathy**

(EIEE: Ohtahara syndrome)

**Early Myoclonic Encephalopathy (EME)**
EIEE (Ohtahara Syndrome)

- Newborn or first 3 months of life
- Tonic spasms (isolated or clusters)
- Partial seizures (30-50%)
- Myoclonic seizures (rare)
- EEG: BS pattern (awake/sleep)
- Abnormal neuroimaging
- Resistant to AEDs
- Poor neurodevelopmental outcome
<table>
<thead>
<tr>
<th></th>
<th>EIEE</th>
<th>EME</th>
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</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Brain malformation</td>
<td>Genetic and Metabolic</td>
</tr>
<tr>
<td><strong>Clinical sz</strong></td>
<td>Tonic spasms</td>
<td>Erratic myoclonic, focal sz</td>
</tr>
<tr>
<td></td>
<td>Focal sz</td>
<td></td>
</tr>
<tr>
<td><strong>EEG: BS</strong></td>
<td>Regular, shorter</td>
<td>Irregular, longer</td>
</tr>
<tr>
<td></td>
<td>Sleep⇔Awake</td>
<td>Predom. sleep</td>
</tr>
<tr>
<td></td>
<td>Hypsarrhythmia</td>
<td>Persist after 1 Y</td>
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<td></td>
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<tr>
<td>Sz evolution</td>
<td>To West synd, LGS</td>
<td>Persistent regression</td>
</tr>
</tbody>
</table>
Burst-Suppression
Burst-Suppression
Early Myoclonic Encephalopathy (EME)

- Mostly within 1 month of birth
- Fragmentary myoclonic seizures
- Partial seizures (frequent)
- Tonic spasms (occasional/transient)
- EEG: BS pattern (enhanced by sleep)
- Inborn error of metabolism
- Intractable to AEDs
- Very poor outcome & high mortality rate
Epileptic Spasms

- Sustained contraction of axial muscles
- Flexion of neck & trunk with abduction and elevation of both arms
- "Salaam position"
- Initial movement relatively fast (myoclonic-like)
- Remain in the Salaam position for few seconds before relaxation
- Duration of each spasm: milliseconds to 5-10 seconds
- In CLUSTER
- Ictal EEG: Diffuse high-voltage slow followed by background attenuation
West Syndrome

- Epileptic (infantile) spasms
- Delayed development
- EEG- Hypsarrhythmia
West Syndrome

- Onset 3-7 months of age
- 1.6-4.3: 10,000 live births
- Spasms- flexor, extensor or mixed
- In clusters, frequently during drowsiness/arousal
- EEG: Hypsarrhythmia
  (chaotic, irregular, diffuse asymmetric, high-voltage, interspersed with sharp waves and spikes)
Hypsarrhythmia
Ictal EEG and EMG during Spasms

Federico Vigevano, Brain & Development 23 (2001) 467–472
# Etiologies of West Syndrome

<table>
<thead>
<tr>
<th>Causes</th>
<th>%</th>
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<tbody>
<tr>
<td>Brain malformation/ Tuberous sclerosis</td>
<td>35</td>
</tr>
<tr>
<td>Perinatal insults</td>
<td>9</td>
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<tr>
<td>Undetermined pre/perinatal factors</td>
<td>19</td>
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<tr>
<td>Infections</td>
<td>2</td>
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<tr>
<td>Hypoglycemia</td>
<td>8</td>
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<tr>
<td>Metabolic causes</td>
<td>9</td>
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<tr>
<td>Idiopathic</td>
<td>18</td>
</tr>
</tbody>
</table>
Benign non-epileptic myoclonus of infancy (Benign non-epileptic infantile spasms)

• Onset 4-12 mo, F=M
• Clusters of spasms during awake and sleep, elicited by excitement, fear, anger, frustration, need to void
• Normal development, normal EEG
• Exaggeration of physiologic myoclonus, same category with shuddering attacks
Myoclonic Epilepsy in Infancy

- 2% of children <3 years with epilepsy
- Neurologically normal
- Onset: 6 months - 2 years
- Family history of epilepsy in 20-25%
- Preceding febrile seizures in 20%
- EEG: gen. SAW or polyspike-waves (drowsiness/early sleep stages) w/photosensitivity
- AEDs: VPA
- Educational difficulties (20-40%)
Severe Myoclonic Epilepsy of Infancy (SMEI)

- Dravet syndrome
- 1:20,000-1:40,000 infants
- Boys>girls
- Neurodevelopment intact prior to onset
- 1\textsuperscript{st} year: gen/unilateral clonic or GTC asso. with fever
- 2\textsuperscript{nd} year: myoclonic seizures
- Progressive regression, hyperactivity
Dravet syndrome (Ds)
(Severe myoclonic epilepsy of infancy-SMEI)
SCN1A, SCN2A, SCN1B, and GABRG2, SCN9A as modifier

- GEFS+
  - SCN1A, SCN2A, SCN1B, GABRD, and GABRG2

- FS/FS+
  - FEB1, FEB2, SCN1B, SCN1A, GABAA, GABRG2

- SIMFE
  - SCN1A

- EMRF
  - PCDH19

- SMEI-Borderland
  - SCN1A

- ICE-GTC
  - SCN1A
Severe Myoclonic Epilepsy of Infancy (SMEI)

- Highly intractable to AEDs
  - Useful AEDs: VPA, Benzodiazepines (CNZ, Clobazam, Lorazepam), Stiripentol
  - Alternative: ZNS, VGB, Ketogenic diet
  - Avoid: LTG?, PHT, CBZ
- Prognosis is very poor
Thank You for Your Attention