Epilepsies and Electroclinical Syndromes: Neonatal and Infantile

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Objectives

- Overview of early-life epilepsy syndromes:
  - Self-limited
  - Developmental and Epileptic Encephalopathies

- Clinical and EEG features, treatment and prognosis
Epidemiology of Early Life Epilepsies

Wirrell et al. 2011
Many early-life epilepsies are considered DEEs

- Developmental encephalopathy
  - Due to underlying etiology
  - Not improved with better seizure control but may be helped with precision therapies

- Epileptic encephalopathy
  - Epileptic activity itself contributes to profound neurological and cognitive impairment, thus improved with better seizure control
Identifying *syndrome* and/or *etiology* may help to select the optimal therapy

- **SCN1A (Dravet)**
  - Use STP, CBD, FFA, avoid Na channel agents
- **TSC – VGB**
- **KCNQ2 and ezogabine**
- **KCNT1 and quinidine**
- **GRIN2A/2D and memantine**
- **SCN2A and SCN8A and phenytoin**

Self-limited Neonatal Epilepsy
(familial and non-familial)

- Usual onset 2-7 days of age, otherwise well baby
- Focal clonic or focal tonic seizures, often with apnea/cyanosis, changing lateralization
- EEG:
  - normal, focal or multifocal discharges
  - Theta pointu alternant interictal pattern in 50% - runs of nonreactive theta, often intermixed with sharp waves, frequently with interhemispheric asynchrony
Theta pointu alternant
Self-limited Neonatal Epilepsy (familial and non-familial)

- Imaging normal

- Genetics: AD with incomplete penetrance. KCNQ2, KCNQ3 or SCN2A

- Usually resolves by 6 mos. Approx 10% may have seizures in later life
Self-limited Infantile Epilepsy (familial and nonfamilial)

- Onset between 3-20 months in neurologically normal infants
- Seizures are often frequent, focal (typically posterior onset), occur in clusters over several days and may secondarily generalize
Self Limited Infantile Epilepsy

- Interictal EEG: normal or posterior EDs
- Imaging is normal
- Genetic studies often positive – PRRT2 (90%), SCN2A, KCNQ2, KCNQ3
- Pharmacoresponsive and remit within 6-24 months
- Difficult to diagnose with certainty if genetics are negative, need careful follow-up to ensure epilepsy course is consistent with this diagnosis
Myoclonic Epilepsy of Infancy

- Rare compared to IS - ≈ 2% of epilepsies with onset before age 3 years
- Massive myoclonic jerks occurring singly or in brief cluster, in neurologically normal child between 4 mos and 3 yrs, often at sleep transitions
- Subgroup with reflex-induced seizures
- Positive family history for epilepsy or febrile convulsions in 30%
Myoclonic Epilepsy of Infancy

- **EEG:**
  - GSW maximal in sleep; photosensitivity may be seen

- **Treatment:**
  - Pharmacoresponsive (benzos, LEV or VPA)
  - AEDs can be weaned after 1-2 years

- **DDx:**
  - Benign myoclonus of infancy (normal EEG)
  - Infantile spasms
  - Other myoclonic epilepsy syndromes (Dravet, MAE)
  - Metabolic disorders
Genetic Epilepsy with Febrile Seizures Plus

- AD with incomplete penetrance, 2 or more family members affected
- **Semiology varies:**
  - FS and FS+ (persist beyond 6 yrs of age)
  - Focal or generalized afebrile seizures
  - Epileptic encephalopathies (Dravet, MAE)
  - Most are self-limited and pharmacoresponsive
Genetic Epilepsy with Febrile Seizures Plus

- EEG – nonspecific, may show GSW
- Neuroimaging normal if done
- Treatment: based on seizure semiology/frequency/syndrome
Developmental and Epileptic Encephalopathies
Early Infantile DEE

- Encompasses former Early Myoclonic Encephalopathy and Ohtahara syndrome
- Onset in first 3 months of life
- Abnormal neurological exam – tone, movement disorders, cortical visual impairment
- Moderate to severe ID with time
EIDEE – Seizures

- Very frequent, drug-resistant
- Seizure types vary – often several types:
  - Focal or generalized tonic – often in clusters
  - Myoclonic – erratic or massive bilateral
  - Spasms
  - *Sequential* seizures – progress in a sequential manner with tonic, clonic, myoclonic or spasms following each other, without a single predominant feature
  - Focal clonic
EIDEE

- EEG very abnormal and typically deteriorates shortly after seizure onset
  - Burst suppression or diffuse slowing with multifocal discharge
- Imaging – **structural** brain abnormalities are important and frequent causes
3 month old boy with focal spasms and focal clonic seizures
Right Hemimegalencephaly
EIDEE

- Genetic etiologies are found in >50% and may co-exist with abnormal neuroimaging

- Metabolic studies should be considered, particularly if MRI is normal
CDKL5 Hypermotor-tonic-spasm

Klein et al. Neurology
2011
Epilepsy in Infancy with Migrating Focal Seizures

- Very frequent, multifocal seizures, often with autonomic features, onset <6 months
- Developmental plateau/regression
- Etiology:
  - often unknown
  - genetic mutations in a minority (KCNT1, SCN1A, SCN2A, SCN8A, and PLCB1)
  - MRI may be normal at onset but shows atrophy with time
EIMFS: Seizures show a migration pattern clinically or on EEG
EIMFS

- Treatment dictated by genetic mutation:
  - SCN2A and SCN8A – high dose phenytoin
  - KCNT1 - quinidine
  - Other options: levetiracetam, clobazam, rufinamide, ketogenic diet, stiripentol, bromides

- Long term prognosis for development and seizure control is poor
West (Infantile Spasms) Syndrome

- Most common severe epilepsy in first year of life (1 in 5000)
- Peak onset 3-9 months
- Seizures:
  - Clusters of spasms, characteristically shortly after waking
- Development:
  - Delay often precedes spasms
  - Often regress after spasm onset
West Syndrome

- **EEG**
  - 90% have hypsarrhythmia interictally (should record nREM sleep)
    - High amplitude, slow background with multifocal discharge (*Mytinger et al. 2015*)
    - BUT lack of hypsarrhythmia should not change your treatment plan! (*Demarest et al. 2017*)
  - Ictal: slow wave preceded or followed by electrodecrement
Improving inter-rater reliability of hypsarrhythmia – BASED score

<table>
<thead>
<tr>
<th>BASED score</th>
<th>Description</th>
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<tbody>
<tr>
<td>NA</td>
<td>When using five minute epochs, EEG grade 0 (normal) and 1 (any definite nonepileptiform abnormality) cannot be used</td>
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<tr>
<td>≤2</td>
<td>&lt;3 spike foci AND no common background slow waves ≥200 μV&lt;sup&gt;b,c&lt;/sup&gt;</td>
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<tr>
<td>3</td>
<td>MFS &lt;50% of one second bins&lt;sup&gt;a&lt;/sup&gt; and no common background slow waves ≥200 μV&lt;sup&gt;b,c&lt;/sup&gt;, OR no MFS but common background slow waves ≥200 μV&lt;sup&gt;b,c&lt;/sup&gt;</td>
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<tr>
<td>4&lt;sup&gt;e&lt;/sup&gt; Hypsarrhythmia</td>
<td>MFS &lt;50% of one second bins&lt;sup&gt;a&lt;/sup&gt; AND common background slow waves ≥200 μV&lt;sup&gt;b,c&lt;/sup&gt;</td>
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<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt; Hypsarrhythmia</td>
<td>MFS ≥50% of one second bins&lt;sup&gt;a&lt;/sup&gt;, OR common background slow waves ≥300 μV&lt;sup&gt;b,d&lt;/sup&gt; in two or more bilateral head regions</td>
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Mytinger et al. 2015
West Syndrome
Etiology

- 20-30% - unknown

- 70-80% - known cause:
  - Structural – malformation or acquired
  - Genetic
  - Less commonly metabolic, infectious
West Syndrome: Treatment

- First line agents:
  - Vigabatrin (150 mg/kg/d) – best if TSC or FCD
  - ACTH (150 U/m2) or high dose oral prednisolone (4-8 mg/kg/d, max 60 mg) – likely are similarly efficacious (Grinspan et al. in press)
  - Combination therapy most efficacious to stop spasms but did not alter longterm outcome (O’Callaghan et al. 2017)
  - Pyridoxine trial if no clear underlying cause (100 mg/d x 1-2 wks) – should not delay first-line treatment
- TPM, VPA, CLN, ketogenic diet are other options but not first line
West Syndrome: Surgery

- Consider surgical evaluation if first line therapies fail and in whom a focal lesion is known or suspected.
- Lack of classic hypsarrhythmia is more common in TSC or FCD.
- Resections can be more localized or extensive (multilobar or hemispheric).
- Detection of FCD on MRI can be challenging in infants – other imaging modalities may be needed.
West Syndrome: Surgery

Outcomes:

- 58-71% Engel Class 1
- Better cognitive outcomes with shorter duration of epilepsy and presence of MRI lesion

West Syndrome

Prognosis

- Etiology matters:
  - Unknown cause - 40-50% good outcome
  - Known cause - >95% ID
- Risk of ASD longer term
- Spasms typically resolve by 1 year of age but are often replaced by other seizure types
- Longer the lag to effective treatment = poorer prognosis
Dravet Syndrome

- 5% of all early onset epilepsy
- Seizure types:
  - Recurrent, prolonged, hemiconvulsive seizures with fever in first year
  - Other seizure types onset between 1-6 years of age (myoclonus, atypical absences, focal seizures)
- Development:
  - normal prior to seizure onset
  - plateaus and rarely regresses in preschool years
- Most develop ataxia, pyramidal signs and crouch gait
Dravet Syndrome

- EEG
  - Abnormal by age 2 years
  - Slow background
  - Focal, multifocal or generalized d/c
  - Some show early photosensitivity

- Imaging and metabolic studies are normal

- 80% have SCN1A mutation (often truncated protein) – but not all SCN1A mutations lead to Dravet syndrome

- Treatment:
  - VERY resistant to ASMs
  - Older standards: clobazam, valproic acid, topiramate, ketogenic diet,
# Dravet Syndrome: New Treatment Options

<table>
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<tr>
<th>Study</th>
<th>&gt;50% reduction in seizures</th>
<th>&gt;75% reduction in seizures</th>
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<tr>
<td>Fenfluramine vs Placebo</td>
<td>70% vs 7.5%</td>
<td>45% vs 2.5%</td>
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<tr>
<td>Cannabidiol vs Placebo</td>
<td>43% vs 27%</td>
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<tr>
<td>Stiripentol vs Placebo</td>
<td>71% vs 5%</td>
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Dravet: Prognosis

- Seizures are pharmacoresistant
- By early adolescence/adulthood: brief, nocturnal GTCS continue but other seizures have resolved
- ID in all but severity varies – worse outcome if longer use of CIM (**de Lange et al. 2018**)
- High risk of SUDEP
- Parkinsonian features as adults
Hemiconvulsions, Hemiplegia, and Epilepsy Syndrome (HHE)

- Rare, onset <4 yrs with prolonged unilateral SE with febrile illness followed by immediate hemiplegia
- Months-years later - intractable focal epilepsy
- EEG – slowing and EDs over affected hemisphere
- MRI – edema of affected hemisphere at time of initial SE, then progressive atrophy
- Hemispherotomy often required
Conclusions: Early-life Epilepsies

- High rates of intractability (1/3) and significant neurological disability
- Identifying etiology and syndrome assists with prognosis and informs best therapy
- Genetic testing is high yield
- Consider surgical evaluation if medically intractable and possible focal structural lesion
  - TIME is BRAIN