Genetically Determined Epilepsy Syndromes

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Disclosure

Investigator: NIH, Autism Speaks, HRSA, SFARI
Epilepsy: Incidence/100,000

Hauser, Epilepsia 33:1992
Epilepsy: Etiology vs. Age of Onset

- Perinatal injury
- Metabolic defect
- Congenital malformation
- Infection
- Genetic epilepsy
- Postnatal trauma
- Brain tumor
- Vascular disease

**Age (yr)**

- Birth
- 2
- 3
- 5
- 10
- 20
- 30
- 50
- 70
# Epilepsy Treatments

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Indication</th>
<th>Efficacy</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEDs</td>
<td>Children and adults</td>
<td>Specific AEDs for specific seizure types</td>
<td>~64% seizure-free (SF)¹</td>
<td>Varies by AED</td>
</tr>
<tr>
<td>Ketogenic Diet</td>
<td>Primarily early childhood</td>
<td>All seizure types, typically intractable seizures</td>
<td>54% &gt;50% seizure reduction @ 3 mos²</td>
<td>Lipid disorder, ketoacidosis</td>
</tr>
<tr>
<td>Epilepsy Surgery</td>
<td>Children and adults</td>
<td>Pharmaco-resistant and localization-related epilepsy</td>
<td>~70% SF in select patients³</td>
<td>Surgery-related risks; varies by location of surgery</td>
</tr>
<tr>
<td>Vagus Nerve Stimulator</td>
<td>12 yrs and older*</td>
<td>Pharmaco-resistant and partial seizures*</td>
<td>43% &gt;50% seizure reduction at 3 yrs⁴</td>
<td>Voice alteration, cough, pharyngitis, dyspnea</td>
</tr>
</tbody>
</table>

* FDA-approved
Genetic Testing Principles

Dravet and related syndromes

- Mutation testing is available for SCN1A, SCN1B, and GABRG2
- Testing is not recommended for non-SMEI forms of GEFS+ or myoclonic astatic epilepsy

Infantile Spasms

- Many causes guided by clinical features and imaging
- Molecular and cytogenetic testing is recommended if no obvious etiology is present.
<table>
<thead>
<tr>
<th>Genetic Testing Principles</th>
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<tbody>
<tr>
<td><strong>Common Idiopathic epilepsy</strong></td>
</tr>
<tr>
<td>- Routine tests for autosomal dominant nocturnal frontal lobe epilepsy are available.</td>
</tr>
<tr>
<td>- No useful test exists for the most common generalized and focal onset idiopathic syndromes.</td>
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</table>
Genetic Testing Principles

Epilepsy with brain malformation

- Tests are guided by clinical features and MRI appearance
- Not all cases of epilepsy with brain malformation have a genetic cause

Epilepsy with Intellectual Disability or Dysmorphia

- Clinical features guide investigation
- Most cases lack specificity except for Miller Dieker syndrome and ring chromosome 20 syndrome.
- Molecular karotyping yield is significant.
The Good: Genetic Epilepsy Syndromes
Generalized Epilepsy Syndromes
GENERALIZED SEIZURES
IGE Syndromes

- Generalized Epilepsy without main genes
  - Childhood Absence Epilepsy
  - Juvenile Absence Epilepsy
  - Juvenile Myoclonic Epilepsy
Generalized Epilepsy
Febrile Seizures (GEFS+)

- Febrile seizures 3 months to 6 year range
  - Plus febrile seizures outside this range
  - After this range GTC or absence seizure occur. Other seizures types including focal seizures are possible.

- History of febrile seizures in other family members is crucial to diagnosis
Generalized Epilepsy Febrile Seizures (GEFS+)

- Neuro exam is normal but can have cognitive issues
- EEG is either normal, irregular generalized SW or can have focal epileptiform discharges
- Genetics: SCN1A, SCN1B, SCN2A, GABRG2
- Prognosis: Likely remission by puberty
AD Nocturnal Frontal Lobe Epilepsy

- 17 different nAChR genes. Mutations in CHRNA4, CHRNA2, (CHRNA7)

- Onset in late childhood

- Presynaptic receptors that regulate GABA and glutamate release

- EEG- normal or bifrontal slowing +/- SW
AD Nocturnal Frontal Lobe Epilepsy

- Diagnosis: seizures with hyperkinetic limb movements or tonic limb posturing during NREM sleep
- Confused with nocturnal parasomnias
- Seizures remit over time.
Familial TLE

AD Lateral Temporal Lobe Epilepsy

- Chromosome 10q24 containing LGI1 gene
- 50% have this mutation
- Auditory hallucinations (ringing, humming, whistling, buzzing) plus ictal aphasia. All symptoms are often followed by 2ndarily GTC seizure.
- Onset: late adolescence
Familial TLE

Familial MTLE

- Pure form- not associated with febrile seizure or hippocampal sclerosis
- Pure form-linked to chromosome 4q13.2-21.3 in AD incomplete penetrance fashion
- Familial forms –MTLE + MTS or MTLE + FS

- Linked to more than a dozen genes including interleukins, GRIN1, SCN3A, SCN3B
The Bad: Dravet Syndrome
Dravet’s Syndrome

- **Severe Myoclonic Epilepsy of Infancy**
  - First described by Dravet in 1982
  - Genetics:
    - Missense and truncation mutations in SCN1A
    - Voltage gated Na channel subunit gene
    - Present in >70% of patients
Dravet’s Syndrome

- Severe Myoclonic Epilepsy of Infancy
  - First described by Dravet in 1982
  - Genetics:
    - Missense and truncation mutations in SCN1A
    - Voltage gated Na channel subunit gene
    - Present in >70% of patients
  - Progressive Course:
    - Developmentally normal or mildly delayed
    - Febrile status epilepticus
    - Afebrile generalized and unilateral clonic seizures
    - Development of myoclonus, atypical absence, partial seizures
    - Significant cognitive and developmental deterioration, eventually nonverbal and nonambulatory
Dravet’s treated with Keto diet
Angelman syndrome (Happy Puppet Syndrome)

- Severe developmental delay with absent speech
- Happy disposition with paroxysms of laughter
- Wide based gait
- Jerky movements, myoclonus, or tremors
- Atypical absences
- Myoclonic seizures
- GTC seizures
- Partial seizures
Angelman syndrome

- Genetics
  - 70% have a type 1 or type 2 deletion (~4 Mb) of 15q11-q13
  - UBE3A mutations
  - Methylation imprinting
  - Uniparental disomy

- EEG
  - Diffuse bilateral frontal predominant high amplitude notched delta slowing
  - Sharp waves or Spikes (2-2.5 Hz)
  - Posterior quadrant theta slowing elicited by eye closure
Angelman syndrome
Rett Syndrome

- Deletions or duplications of MECP2 gene
- FoxG1 gene
- Normal development until between 6-18 months
- Regression characterized by ataxia and hand wringing movement
- Cognitive decline
- Autistic features
- Acquired microcephaly
Rett Syndrome

Seizure types
- Onset 2-3 years
- *Complex partial seizures
- Myoclonic/GTC seizures
- Tonic/Atonic seizures
- <Absence/clonic seizures
- EEG
- Progressive slowing
- With needle like central spikes (activated by SS stimuli)
- 4-6 Hz rhythmic central theta

EEG patterns Vary with Stage

Discharges in centrottemporal regions

Rhythmic generalized spike activity

Slow theta rhythm
Ring Chromosome 14

- Dysmorphia, Microcephaly, plus ocular findings (retinal dystrophy)
- Onset of seizures - 1st year of life
- Pharmacoresistant GTC seizures, complex partial seizures, minor motor seizures
- Seizures with fever and clusters
- Focal spikes, focal slowing, multifocal spikes on interictal EEG
Ring Chromosome 20

- Initially normal development before seizures
- Onset - in childhood
- Mild to moderate intellectual disability
- Pharmacoresistant frontal lobe seizures
- Characteristic NCSE - partial or generalized

- Ictal EEG - frontal temporal theta
- Interictal-diffuse 1-2 Hz background slowing + frontal SW
- Breakpoint are 20q13 - location of CHRNA4 (ADNFLE) and KCNQ2 (BFNS)
Glucose Transporter Deficiency (GLUT-1)

- AD
- Loss of functional glucose transporters across the BBB
- CSF glucose 30-40 mg/dl
- Low serum lactate
- Mutation in GLUT-1 gene

- Refractory epilepsy & developmental delay
- Neonatal period
- Infantile epilepsy
- Absence seizures
- Myoclonic seizures
- Astatic seizures
- GTC seizures
Glucose Transporter Deficiency (GLUT-1)

- Ataxia
- Hypotonia
- Acquired Microcephaly
- Atypical presentations
- Childhood absence epilepsy
- Paroxysmal exertional dyskinesia
- Normal EEG between seizures
- > 2 yrs old 2.5-4 Hz generalized SW
- 10% have no clinical seizures
- Treatment-ketogenic diet
The UGLY: Mitochondrial Disorders & Progressive Myoclonic Epilepsies
Progressive Myoclonic Epilepsy Syndromes

- **Clinical:**
  - As a group, present in middle of childhood, 8-13 yrs
  - NCL presents in infantile forms
  - Characterized by severe myoclonic epilepsy, in addition to other seizure types
  - Progressive neurologic deterioration

- **EEG:**
  - Diffuse theta activity
  - Ictal activity: 3-5 Hz Gen SW and PSW
  - Late in course, EEG “burns out”
PME: NCL
## Progressive Myoclonic Epilepsy Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Chromosome</th>
<th>Gene</th>
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<tbody>
<tr>
<td>Unverricht-Lundborg</td>
<td>21q22</td>
<td>Cystatin B</td>
</tr>
<tr>
<td>MERRF</td>
<td>mt DNA</td>
<td>t-RNA LYS</td>
</tr>
<tr>
<td>Lafora disease</td>
<td>6q24</td>
<td>Tyrosine Phosphatase</td>
</tr>
<tr>
<td>Infantile NCL</td>
<td>11p15</td>
<td>Lysosomal peptidase</td>
</tr>
<tr>
<td>Infantile NCL variants</td>
<td>13q, 15q</td>
<td>Membrane proteins ?</td>
</tr>
<tr>
<td>Juvenile NCL</td>
<td>16p</td>
<td>Hydrophobic pt</td>
</tr>
<tr>
<td>Sialidosis type I</td>
<td>6p21</td>
<td>Neuraminidase</td>
</tr>
<tr>
<td>Sialidosis type II</td>
<td>20q13</td>
<td></td>
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</tbody>
</table>
Mitochondrial Disorders

- Any neurologic symptoms combination can be due to mito disorder
- Refractory epilepsy is common (IS, myoclonic, EPC)
- 20% maternal inheritance
- 80% autosomal recessive nuclear genes
- Lactate/raised alanine in serum or CSF is helpful when present
- Multi-organ involvement
- PDH deficiency
- PC deficiency
- Leigh syndrome
# Mitochondrial Disorders

## MERRF
- Mutation in mt tRNA for lysine
- Myoclonic epilepsy
- GTC seizures
- Focal clonic and atonic seizures can be present
- Clinical seizures correlated with SW or polyspike wave complexes

## MELAS
- mtDNA mutation in MTTL1
- Focal seizures from temporal or occipital lobes (motor > visual > temporal semiology)
- Myoclonus/absence szs
- Status epilepticus
- EEG- spikes in parietal-occipital areas or frontal central area
## Mitochondrial Disorders - PolG mutations

### MS CAE
- Spinocerebellar ataxia, peripheral neuropathy, and epilepsy
- +/- Liver failure
- Refractory simple focal seizures in visual hemifield symptoms
- Focal clonic or myoclonic szs
- Status epilepticus
- Localized SW or rhythmic focal slowing

### Alpers-Huttenlocher
- Infants present with partial or generalized status epilepticus
- +/- Liver failure
- Poor survival-few months to several years
- Similar seizure types and EEG findings to MS CAE
- MRI findings usually involve the occipital lobe
Genetically Determined Epilepsy Syndromes

- **Good:** Genetic Epilepsy Syndromes
  - Relatively straightforward treatment
  - CAE, JAE, JME, GEFS+, ADNFLE, Familial TLE
  - Not “benign” neurocognitively: need screening

- **Bad:** can be progressive
  - Dravet (SMEI), Angelman syndrome, Rett, Ring Chromosome, GLUT-1

- **Ugly:** Progressive Epileptic Encephalopathies:
  - Mitochondrial disorders, Progressive Myoclonic Epilepsies
Questions?