The Epilepsies Formally Known as “Generalized”

Martin Gallagher MD, PhD
Associate Professor
Department of Neurology, Epilepsy Division
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Disclosures

I have no relevant financial disclosures

Medications should be assumed to be “off label” unless otherwise indicated
Syllabus for ABPN Epilepsy Boards

Classification 7-9%
Evaluation & EEG 38-46%
Management 38-42%
Mechanisms 7-9%
Therefore, this lecture will focus on the classification, management, evaluation and mechanisms associated with six “generalized” epilepsy syndromes including:

- Childhood absence epilepsy (CAE)
- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with Generalized Tonic Clonic Seizures Alone (EGTC)
- Reflex epilepsies
- Lennox Gastaut
## Classification: Epilepsies formally known as “Idiopathic Generalized”

<table>
<thead>
<tr>
<th>1989 Classification “Idiopathic”</th>
<th>2010 Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign neonatal familial convulsions</td>
<td>Benign familial neonatal epilepsy</td>
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<tr>
<td>Benign neonatal convulsions</td>
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<tr>
<td>Benign myoclonic epilepsy in infancy</td>
<td>Myoclonic epilepsy in infancy</td>
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<tr>
<td>Childhood absence epilepsy</td>
<td>Childhood absence epilepsy</td>
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<tr>
<td>Juvenile absence epilepsy</td>
<td>Juvenile absence epilepsy</td>
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<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>Juvenile myoclonic epilepsy</td>
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<tr>
<td>Epilepsy with grand mal (GTCS) seizures on awakening</td>
<td>Epilepsy with generalized tonic-clonic seizures alone</td>
</tr>
<tr>
<td>Other generalized idiopathic epilepsies not defined above</td>
<td></td>
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<tr>
<td>Epilepsies with seizures precipitated by specific models of activation</td>
<td>Reflex epilepsies</td>
</tr>
</tbody>
</table>
### Epilepsies formally known as “Cryptogenic/Symptomatic Generalized”

<table>
<thead>
<tr>
<th>1989 Classification “Cryptogenic/Symptomatic”</th>
<th>2010 Classification</th>
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<tbody>
<tr>
<td>West syndrome</td>
<td>West syndrome</td>
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<tr>
<td>Lennox-Gastaut syndrome</td>
<td>Lennox-Gastaut syndrome</td>
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<tr>
<td>Epilepsy with myoclonic-astatic seizures</td>
<td>Epilepsy with myoclonic-atonic seizures</td>
</tr>
<tr>
<td>Epilepsy with myoclonic absences</td>
<td>Epilepsy with myoclonic absences</td>
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<tr>
<td>Early myoclonic encephalopathy</td>
<td>Early myoclonic encephalopathy</td>
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<tr>
<td>Early infantile epileptic encephalopathy with suppression burst</td>
<td>Ohtahara syndrome</td>
</tr>
<tr>
<td>Other symptomatic generalized epilepsies not defined above</td>
<td></td>
</tr>
</tbody>
</table>
Childhood Absence Epilepsy Evaluation

Epidemiology

- Age of onset: 4-10 years (peak 5-7 years)
- Prevalence: ranges from 0.1-0.7 / 1000 people
- Female predominance (0.15/1000 boys; 0.48/1000 girls, Waaler, Epilepsia, 2000)
Childhood Absence Epilepsy Evaluation

Clinical features

• Absence seizure: abrupt and severe loss of consciousness
• The eyes spontaneously open; overbreathing, speech, and other voluntary activity stop within the first 3 seconds from the onset of the discharge.
• Automatisms are frequent but have no significance in the diagnosis.
• Eyes stare or move slowly, and random eyelid blinking (usually not sustained) may occur.
• Duration 4-20 seconds
Childhood Absence Epilepsy Evaluation
Two Diagnostic Criteria

**ILAE criteria**
- Onset of typical absence (TA) seizures before puberty
- Normal neuromotor development when TA occurred
- Absence seizures initial type of seizures
- Very frequent TA seizures occurring many times/day
- TA associated with symmetric 3 Hz SWD

**Panayiotopoulos’ criteria**
- Many brief ~ 10 s TA/day - severe consciousness impairment
- Age > 4 y < 10 y
- EEG: 3 Hz SWD (no more than double spike) with gradual run down of frequency
- No other seizures such as GTCS or myoclonic jerks
- No absences with marked eyelid or perioral myoclonus
- No absence with mild impairment of consciousness
- No stimulus sensitive absences.
Childhood Absence Epilepsy Evaluation

EEG

- Spike-wave 3.4 - 4.5 Hz onset & slows to 2.5-2.8 Hz end
- Eye opening alerting may terminate bursts
- NREM sleep increases # spike-wave bursts & changes morphology - reduced duration, fragmented irregular
- Hyperventillation increases spike-wave in 50-80% patients, photic 18%
- OIRDA 70% CAE children between 6-10 years old, rare > 15 years

Pedley, *Current Practice Clinical Electroencephalography*, 2003
Childhood Absence Epilepsy Management

Ethosuximide more efficacious than lamotrigine and better tolerated than valproic acid
Childhood Absence Epilepsy Management

Prognosis

- Prognosis depends on diagnostic criteria used to establish CAE.
- Patients diagnosed with stricter Panayiotopoulos’ criteria had:
  - Higher rates of seizure control (95% vs. 77%)
  - Higher rates of seizure freedom off medication (82% vs. 51%)
  - Fewer GTC (8% vs. 30%)

Groso, Epilepsia, 2005
Childhood Absence Epilepsy Mechanisms
Genetics - Family History

- monozygotic twins: 84% had 3-Hz spike-waves & typical absence in 75%
- dizygotic twins: 16 times less often
- First degree relatives: 17%

## Childhood Absence Epilepsy Mechanisms
### Genetics – Ion Channel Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Abnormalities</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CACNAIH</td>
<td>T-type calcium channel alpha-1H subunit</td>
<td>Multiple missense mutations</td>
<td>CAE in multiple Chinese patients</td>
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<tr>
<td>CACNA1G</td>
<td>T-type calcium channel alpha-1G subunit</td>
<td>Three missense mutations</td>
<td>Japanese patients with CAE or CAE that progressed to JME</td>
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<tr>
<td>GABRA1</td>
<td>$\text{GABA}_A$ receptor $\alpha_1$ subunit</td>
<td>De novo frameshift</td>
<td>One patient with CAE</td>
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<tr>
<td>GABRB3</td>
<td>$\text{GABA}_A$ receptor $\beta_3$ subunit</td>
<td>Haplotype association, missense mutations</td>
<td>Multiple Austrian &amp; Mexican CAE patients</td>
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<tr>
<td>GABRG2</td>
<td>$\text{GABA}_A$ receptor $\gamma_2$ subunit</td>
<td>Missense and insertion</td>
<td>CAE + febrile seizures</td>
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</table>
Childhood Absence Epilepsy Mechanisms
Genetics – Non-Ion Channel Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Abnormalities</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>JRK/JH8</td>
<td>JRK jerky homolog</td>
<td>Missense mutation</td>
<td>CAE evolving into JME</td>
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<tr>
<td>LGI4</td>
<td>Leucine-rich glioma inactivated 4</td>
<td>Polymorphism</td>
<td>42 CAE patients</td>
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<td>SLCA1</td>
<td>Glut1 glucose transporter</td>
<td>Multiple missense</td>
<td><em>early onset</em> absence epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mutations &amp; insertion</td>
<td></td>
</tr>
</tbody>
</table>

For a review, see Yalçın, Seizure, 2012
Childhood Absence Epilepsy Mechanism
Animal models & Pathophysiologyn

Multiple animal models: inbred rats & mice (GAERS, Wag/Rij), genetically modified mice with human CAE mutations, drug-evoked seizures

Blumenfeld, Epilepsia, 2003
Juvenile Absence Epilepsy Evaluation

Epidemiology

Age of onset: 7-17 years (peak 10-12 years)
Prevalence not well studied – diagnosis often overlooked
Estimated 0.1 / 1000 people (Sidenvall, Acta Paediatr 1993)
Juvenile Absence Epilepsy Evaluation

Clinical features

JAE definition mainly based on age of onset & sz frequency

• Absence seizures similar quality as CAE
  • Language function less rapidly abolished?
  • Consciousness less severely impaired?
• Seizure frequency lower than CAE (< 1 /day)
• Frequent association with GTCs

Juvenile Absence Epilepsy Evaluation
Clinical Descriptions

ILAE 1989
• Absences same as in CAE, but less common retropulsive movements
• Manifestation ~ puberty
• Seizure frequency lower than CAE
• Association GTC frequent. GTC may precede absence. Often GTC on awakening.
• Myoclonic seizures
• Sex distribution equal
• Spike-wave often > 3Hz
• Response to therapy excellent

Panayiopoulos 2010
• absence seizures with severe impairment of consciousness.
• Probable GTC
• 1/5 with myoclonic jerks, but mild and no circadian distribution
• 3-4 Hz generalized spike-polyspike-slow waves > 4s severe impairment of consciousness and automatisms.
• No marked eyelid or perioral myoclonus with absences
• No irregular SWD or brief discharges
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Juvenile Absence Epilepsy Evaluation

EEG

- Ictal discharges may be longer than in CAE
- OIRDA uncommon in JAE
- Hyperventillation equal in CAE and JAE
- Photic stimulation less activating in JAE than CAE
Juvenile Absence Epilepsy Management

- Ethosuximide for absence. Likely will need AEDs such as lamotrigine or valproate for other seizure types
- Levetiracetam: - indication for adjunct treatment of myoclonic seizures in JME & primary GTC in “IGE”
- Response to therapy good
  - 100% seizure free if only absences
  - 87% seizure free if \( \leq 10 \) GTC
  - 76% seizure free if \( > 10 \) GTC
  - 62% JAE seizure free 2 years, 56% CAE
- AED withdrawal? One study AED withdrawal unsuccessful when attempted in 8 patients.

Juvenile Absence Epilepsy Mechanism
Genetics & Family History

- Phenotypic concordance within families of JAE 10%
  - Lower than other genetic epilepsy syndromes

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<th>Gene</th>
<th>Protein</th>
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<tr>
<td>EFHC1</td>
<td>EF-Hand Domain (C-Terminal)-Containing Protein 1</td>
<td>Two missense mutations C259Y, I174V</td>
<td>JAE</td>
</tr>
</tbody>
</table>
Juvenile Myoclonic Epilepsy Evaluation

Epidemiology

- Age of onset 8-26 years (typically 12-18 years)
  - diagnosis can occur in 20s or later
  - myoclonic epilepsy in 30s has been reported
- Possible female predominance
- Diagnosis often made retrospectively
- Estimate 0.1-0.2/1000 (Sidenvall Acta Paediatr 1993, Endziniene, Brain Dev 1997)
Juvenile Myoclonic Epilepsy Evaluation
Clinical presentation

- Myoclonic seizures – often shortly after awakening
  - Many patients do not realize they have myoclonic seizures
- Most patients have GTC – selection bias?
- 1/3 absence seizures
Juvenile Myoclonic Epilepsy Evaluation

Interictal EEG

- abundant polyspike complexes
- Spike-wave and polyspike-wave 3.5-6 Hz
- Sensitivity of interictal EEG high: 73%-100%
  - Better for untreated (100%) than treated (63%)
- Hyperventilation activates epileptiform
- Photosensitivity 27-41%
  - Girls 2-3 X more sensitive than boys
- Stage 2 NREM sleep suppressed discharges
Juvenile Myoclonic Epilepsy Evaluation
Myoclonic Ictal EEG

Myoclonic seizures associated with polyspike or polyspike-wave

Pedley, Current Practice Clinical Electroencephalography, 2003
Juvenile Myoclonic Epilepsy Evaluation

EEG - absence CAE, vs. JAE, vs. JME

Absence in JME
- Initial frequency all 3.4-3.5 Hz
- Frequency does not slow at end of discharge in JME
- Multiple spikes; intradischarge variability in JME

Panayiotopoulos, Brain, 1989
Juvenile Myoclonic Epilepsy Management
Pharmacotherapy

- Valproate: Early studies of valproate monotherapy 85-90% seizure control
- Lamotrigine vs. Valproate monotherapy: ~81% of both groups seizure free
- Levetiracetam: - indication for adjunct treatment of myoclonic seizures in JME & primary GTC. Multiple subsequent open label studies showed 50-91% seizure freedom when used as monotherapy
- Topiramate: indication primary generalized seizure monotherapy. Small studies support efficacy for JME

Machado, Seizure, 2013 & Crespel, Epilepsy & Behav, 2013 (Review)
Juvenile Myoclonic Epilepsy Management

Prognosis

- Seizure freedom on AEDs
  - GTC 65-81%
  - Myoclonic 44-65%
- Remission off AEDs 7-17%
- Myoclonic seizures diminish in severity with age

Reviewed in Seneviratne, Epilepsia, 2012
Juvenile Myoclonic Epilepsy Mechanism
Genetics – Family History

• Epilepsy in 1st degree relatives in 39% JME patients – 44% of those were JME

Jayalakshmi, Seizure, 2006
## Juvenile Myoclonic Epilepsy Mechanism
### Genetics – Specific Genes

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<th>Abnormalities</th>
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<tbody>
<tr>
<td>CACNB4</td>
<td>β4 isoform voltage-activated Ca\textsuperscript{2+} channels</td>
<td>R482X nonsense mutation</td>
<td>1JME patient</td>
</tr>
<tr>
<td>CASR</td>
<td>Calcium channel sensor receptor</td>
<td>R898E &amp; 4 rare variants</td>
<td>One family w/ several JME patients and other unrelated JME patients</td>
</tr>
<tr>
<td>GABRA1</td>
<td>GABA\textsubscript{A} receptor α\textsubscript{1} subunit</td>
<td>A322D</td>
<td>1 autosomal dominant JME family</td>
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<tr>
<td>GABRD</td>
<td>GABA\textsubscript{A} receptor δ subunit</td>
<td>R220H</td>
<td>Homozygous in one JME patient</td>
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<tr>
<td>EFHC1</td>
<td>EF-Hand Domain (C-Terminal)-Containing Protein 1</td>
<td>Multiple mutations</td>
<td>Multiple JME families</td>
</tr>
</tbody>
</table>

Delgado-Escueta, Epilepsy Behav, 2013 (Review)
Epilepsy with GTC alone (EGTC) evaluation

Epidemiology

- Age of onset – 2nd decade
- Incidence 1.8/100,000? Loiseau J, Epilepsia, 1990
Epilepsy with GTC Alone Evaluation
Clinical features & EEG

- GTCS exclusively (or > 90%) shortly after awakening (regardless of time of day)
- Possible GTC in relaxed wakefulness in evening
- If other seizures occur, they are absence or myoclonic
- Significant correlation with photosensitivity
- Bursts of generalized spike-wave (regular or irregular, > 2.5 Hz) with a normal background

ILAE 1989; Camfield, Epilepsy Behav, 2010
Epilepsy with GTC Alone Management
Pharmacotherapy & Prognosis

• Nova Scotia population study (36 pts), AED treatment:
  • CBZ in 25 (8 as the only drug)
  • PB in 25 (6 as only drug)
  • PHT in 9 (1 as the only drug) and
  • VPA valproic acid in 7 (1 as the only drug)
  • 100% seizure free X 4 years
  • 33 attempted AED discontinuation; 75% successful
  • Social problems present

• 55 patients with EGTC + photoparoxysmal response
  • All patients prescribed valproate
  • Seizure freedom at 6, 12, & 36 months (69%, 78%, 86%)
  • After VPA stopped, 47% seizure relapses

Camfield, Epilepsy Behav, 2010; Verrotti Eur J Ped Neurol, 2013
Epilepsy with GTC Alone Mechanism

Family History

- Nova Scotia population study (36 pts), Family History
  - Family history available in 35 patients
  - 21 patients had positive family history
  - 11 patients 1st degree relative
  - 10 patients 2nd degree relative

Camfield, Epilepsy Behav, 2010
Reflex Epilepsies Evaluation
Definition?

- **ILAE 1989:**
  - Grouped in “generalized epilepsies”
  - Epilepsies with seizures precipitated by “specific sensation or perception”
  - Stimuli limited to a single specific stimulus in individual patients
- **Berg 2010 Classification (Epilepsia):**
  - No epilepsies grouped as “generalized” or “focal”
  - “Reflex epilepsies” listed as syndrome, but not defined
- **Engel Epilepsia 2001 & Kasteleijn-Nolst Epilepsia 2012:**
  - Syndrome in which all epileptic seizures are precipitated by sensor stimuli

**Reflex epilepsies**
- Idiopathic photosensitive occipital lobe epilepsy
- Other visual sensitive epilepsies
- Primary reading epilepsy
- Startle epilepsy

*Engel, Epilepsia, 2001*
Under the latest definition, reflex epilepsies include:

- Idiopathic photosensitive occipital lobe epilepsy & other visual sensitive epilepsies
- Primary reading epilepsy
- Startle epilepsy
Reflex Epilepsies Evaluation

Epidemiology

- **Idiopathic photosensitive occipital lobe epilepsy**
  - Rare - case series published -
  - Guerrini, Epilepsia 1995 - 10 patients
  - Politi-Elishkevich, J Child Neurol, 2013 16 patients
  - Age of onset 4-17 years

- **Primary reading epilepsy** - Haykal, Epilepsy Behav 2012
  - Rare -- ~180 cases reported
  - Late puberty → early adulthood
  - Male > Female

- **Startle epilepsy** Panayiotopoulos 2005
  - Very Rare
  - Age of onset 1-16 years; both sexes equally affected
Reflex Epilepsies Evaluation
Clinical Presentation

- **Idiopathic photosensitive occipital lobe epilepsy**
  - Seizures precipitated by television, computer, video games etc.
  - Bright, colorful spot in visual field
  - May be followed by conscious head or eye deviation, epigastric pain, vomiting. Normal or mildly impaired consciousness. May progress to GTC. Often followed by headache

- **Primary reading epilepsy**
  - Almost all seizures precipitated by reading (especially aloud)
  - Focal with motor components involve masticatory muscles
  - May evolve to GTC

- **Startle epilepsy**
  - Most patients static neurological deficit - e.g. infantile hemiplegia
  - Seizures induced by **sudden & unexpected** stimuli
  - ~ 30 s axial tonic posturing - often falls
Reflex Epilepsies Evaluation

EEG

- **Idiopathic photosensitive occipital lobe epilepsy**
  - Normal EEG background
  - bilateral occipital spikes & spike-wave
  - Photoparoxysmal response

- **Primary reading epilepsy**
  - Interictal EEG normal
  - Ictal EEG often obscured by jaw artifact. Spikes/sharp waves with dominant hemisphere predominance

- **Startle epilepsy**
  - Interictal diffuse /focal abnormalities reflecting underlying lesion(s)
  - Ictal initial vertex discharge followed by diffuse attenuation or low voltage rhythmic ~ 10 Hz activity near lesion
Reflex Epilepsies Management

- **Idiopathic photosensitive occipital lobe epilepsy**
  - Good outcome. Most seizure free on CBZ, VPA, PB, LTG
- **Primary reading epilepsy**
  - Excellent control with CLZ and LEV
- **Startle epilepsy**
  - No established drug of choice.
  - CBZ, LTG, CLB, and CLZ have been used with benefit
  - Therapy often unsatisfactory
Reflex Epilepsies Mechanism

- **Idiopathic photosensitive occipital lobe epilepsy**
  - Family history of epilepsy in 11/16 of Politi-Elishkevich, 2013
- **Primary reading epilepsy**
  - Positive family history in ~ 40% of cases
- **Startle epilepsy**
  - None known
Lennox-Gastaut Syndrome Evaluation

Epidemiology

- Age of presentation 1-8 years (peak 3-5 years)
- Prevalence 0.26/1,000 at age 10 years

Trevathan, Epilepsia 1997
Lennox-Gastaut Syndrome Evaluation

Clinical Presentation

• Generalized seizures such as tonic (80%), atonic (65%) and atypical absence (60%)
  • Partial (10%), myoclonic (50%), and GTC also observed
• EEG diffuse, slow spike-wave complexes (<3 Hz) with characteristic paroxysmal fast rhythms of 10-12 Hz in sleep
• Cognitive dysfunction

ILAE, 1989
Lennox-Gastaut Syndrome Evaluation
EEG - slow spike-wave

VanStraten, Ped Neurol, 2012
Lennox-Gastaut Syndrome Evaluation
EEG - Paroxysmal Fast Activity

, Wyllie's Treatment of Epilepsy: Principles and Practice 2001
70-80% have known structural lesion - “symptomatic” cause

- Brain malformation
- Hypoxicischemic encephalopathy
- Meningoencephalitis
- Neurocutaneous syndromes,
- Metabolic syndromes
- 30-65% had previously West syndrome

20-30% Cause unknown. Genetic? Formally called “cryptogenic”
Lennox-Gastaut Syndrome Management
Pharmacotherapy

Valproate often used. In addition....

Clonazepam also indicated for Lennox-Gastaut

VanStraten, Ped Neurol, 2012
Lennox-Gastaut Syndrome Management
Non-pharmacological therapy

• Ketogenic diet: 51% achieved > 50% seizure reduction

• Vagal Nerve stimulator

• Corpus callosotomy: 75-80% have > 50% reduction in GTC and drop attacks

VanStraten, Ped Neurol, 2012
Lennox-Gastaut Syndrome Mechanism
Genetics – screen for de novo mutations

- 20-30% Cause unknown. Genetic?
- Screen for de novo mutations
- 149 patients with West Syndrome & 115 Lennox Gastaut
- Patients had no evidence of acquired epilepsy, and normal development until onset of seizures
- Parents had no evidence of seizures
- Exomes of patients and parents sequenced
- Mutations in 16 genes associated with LGS

Lennox-Gastaut Syndrome Mechanism de Novo mutations in ≥ 2 probands

<table>
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<tr>
<th>Gene</th>
<th>Protein</th>
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<tbody>
<tr>
<td>ALG13</td>
<td>Asparagine linked glycosylation</td>
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<tr>
<td>CDKL5</td>
<td>Cyclin Dependent Kinase Like 5</td>
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<td>GABRB3</td>
<td>$GABA_A$ receptor β3 subunit</td>
</tr>
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<td>SCN1A</td>
<td>Sodium Channel Neuronal Type 1 α Subunit</td>
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<td>SCN2A</td>
<td>Sodium Channel Neuronal Type 2 α Subunit</td>
</tr>
<tr>
<td>SCN8A</td>
<td>Sodium Channel Neuronal Type 8 α Subunit</td>
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<tr>
<td>STXBP1</td>
<td>Syntaxin Binding Protein</td>
</tr>
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</table>

Summary I

• **Classification:**
  - new classification scheme groups epilepsies by age of onset, not focal vs. generalized or idiopathic vs. symptomatic

• **Evaluation:**
  - CAE, JAE, JME, EGTC all can have absence, GTC and myoclonic seizures.
  - Primarily distinguished by age of onset and predominance of seizure types.
  - LGS characterized by age of onset, seizure types & EEG
Summary I

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Summary II

- **Management:**
  - CAE, JAE, JME, EGTC – medications match seizure types. ETX absence. VPA, LTG, & GTCs and VPA & LEV for myoclonic
  - JME - LEV indicated for adjunctive therapy
  - LTG, TPM, CLB, RFM, CLZ, FBM indicated for LGS. VPA also extensively used

- **Mechanism:**
  - Absence (and possibly other generalized) seizures related to thalamocortical oscillations
    - Transient calcium channel currents ($Ca_T$) necessary
  - Specific mutations in ion channel and non-ion channel genes strongly associated with these syndromes