Febrile Seizures and Genetic Epilepsy Syndromes
Goals of Presentation

Review basics of seizures and epilepsy
Learn about febrile seizures
Discuss approach to seizures in children
Become familiar with epilepsy syndromes
Overview of genetics of epilepsy
Reviewing the Basics

Seizure:
- Sudden disruption of the brain’s normal electrical activity.
- Accompanied by altered consciousness, disruption in motor or sensory systems.
- Can be subtle or “silent” (sub-clinical).
- Many different types of seizures.
  - Generalized vs focal
  - Tonic, tonic-clonic, myoclonic, atonic, absence

Epilepsy:
- In 3 words
  - RECURRENT
  - NONPROVOKED
  - SEIZURES
Reviewing the Basics

10%

1%
General approach to childhood seizures

Initial diagnostic evaluation-- “4 questions”

1. Seizure confirmation: “Are the events seizures?”
2. Seizure classification: “Where on the surface of the brain does the seizure originate?”
3. Epilepsy classification: “What is the etiology for these seizures?”
4. Syndrome identification: “Do the seizures and other patient-specific symptoms (eg, age of onset, EEG pattern, developmental status) fit a recognizable pattern?”
1- Seizure Confirmation

Million dollar question #1: Are the events epileptic in nature?

There are many seizure mimickers in children:
- Syncope
- Tics
- Inattentiveness
- Migraine
- Behavioral events

Establishing diagnosis is of paramount importance:
- Non-epileptic seizures do not respond to seizure medications
- Delay in diagnosis results in delay of appropriate treatment
- More difficult to stop an AED than to start one
1- Seizure Confirmation

Million dollar question #2: How can I know if the events are epileptic?

HISTORY!
- Detailed history of events, sequential from before event started to after.
- Helpful if parent can video record event.
- Factors leading toward epileptic seizure vs non-epileptic event?

EEG!
- Only diagnostic study uniformly recommended after new-onset seizure.
- Prolonged or routine?
- Do we have to capture a spell?
2- Seizure Classification

Where in the brain do the seizures originate?

**Focal**

**Generalized**

***Some seizures have focal onset with “secondary generalization”***
2- Seizure Classification

Why important to distinguish focal or generalized?

- may influence work-up (more likely to get MRI if focal onset)
- may influence medical management (focal drugs vs generalized drugs)
- potential surgery (focal resection, hemispherectomy, corpus callosotomy, etc)
2- Seizure Classification

“Simple partial” = focal seizure without impairment of consciousness

“Complex partial” = focal seizure with impairment of consciousness = “focal dyscognitive”
Generalized Tonic-Clonic Seizure

https://www.youtube.com/watch?v=axOSChJWEHA
Generalized Tonic Seizure

https://www.youtube.com/watch?v=pjmDY3tR6ak
Generalized Absence Seizure

https://www.youtube.com/watch?v=obbg1BFt26Q
Generalized Atonic Seizure

https://www.youtube.com/watch?v=9obFVWW47NE
Epilepsy Action

UK charity

http://epilepsy.org.uk/

http://learn.epilepsy.org.uk/training-for-schools
Epilepsy Support in ABQ?

Epilepsy Support & Educational Services
epilepsysupportnm.org
epilepsyNM@gmail.com
(505) 243-9119

Epilepsy Walk

Saturday, March 26th

9 AM – Noon

Tiguex Park (near ABQ Museum of Art, Natural History, Explora)
3- Epilepsy Classification (Etiology)

International League Against Epilepsy (ILAE) classification

Old classification:
- Idiopathic (primary) – presumed genetic etiology
- Symptomatic (secondary) – known or presumed structural or metabolic abnormality
- Cryptogenic – presumed symptomatic but etiology not known

2010 ILAE proposed revision:
- Genetic
- Structural/Metabolic
- Unknown
3- Epilepsy Classification

- **Idiopathic = genetic**
- **Symptomatic = structural/metabolic**
- **Cryptogenic = unknown**

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<tr>
<th>Table 1-1: New Terminology and Concepts Contrasted With Older Terminology</th>
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<tr>
<td><strong>Old Term and Definition</strong></td>
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<tr>
<td>Idiopathic: No underlying cause other than a possible hereditary predisposition exists. Idiopathic epilepsies are defined by age-related onset, clinical and electroencephalographic characteristics, and a presumed genetic etiology.</td>
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<td>Symptomatic: Symptomatic epilepsies and syndromes are considered the consequence of a known or suspected disorder of the CNS. Structural/metabolic: A distinct structural or metabolic condition or disease has been demonstrated to be associated with a substantially increased risk of developing epilepsy in appropriately designed studies.</td>
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<td>Cryptogenic: Refers to a disorder whose cause is hidden or occult. Cryptogenic epilepsies are presumed to be symptomatic, but the etiology is not known. Unknown: Meant to be viewed neutrally and to designate that the nature of the underlying cause is as yet unknown; it may have a fundamental genetic defect at its core or it may be the consequence of a separate or unrecognized disorder.</td>
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*Data from Commission on Classification and Terminology of the International League Against Epilepsy. [Epilepsia](https://pubmed.ncbi.nlm.nih.gov/10.1111/j.1365-2587.2010.05352.x/abstract) 2010;51:3-12.*

Febrile Seizures

A febrile seizure is a seizure accompanied by fever (temperature ≥ 100.4°F or 38°C by any method), without central nervous system infection, that occurs in infants and children 6 through 60 months of age. Febrile seizures occur in 2% to 5% of all children and, as such, make up the most common convulsive event in children younger than 60 months.
Febrile Seizures

6 months – 6 years
Fever (BUT NO CNS INFECTION)
Developmentally normal

Before 6 months? NOT A FEBRILE SEIZURE
After 6 years? NOT A FEBRILE SEIZURE
Simple Febrile Seizure

Criteria:

- primary generalized seizure
- last less than 15 minutes
- no recurrence in 24 hour period (or during duration of febrile illness)
Simple Febrile Seizure

Recommended work-up?

Labs?
Lumbar Puncture?
EEG?
MRI?

“Identify the cause of the fever”

Why important identify fever?

Management for viral syndrome vs UTI vs otitis media vs meningitis
Simple Febrile Seizure

AAP Practice Guidelines from 2011

Subcommittee on Febrile Seizures:
• child neurologist (chair)
• neuroepidemiologist
• 3 additional child neurologists
• practicing pediatrician

Methodology:
• Comprehensive review of evidence-based literature from 1996 to 2009.
• 500+ articles reviewed.
• 70 articles which best fit criteria selected.
Simple Febrile Seizure

Key Action Statements from AAP Guidelines:

**Action Statement 1— Lumbar Puncture**

**Action Statement 1a**

A lumbar puncture should be performed in any child who presents with a seizure and a fever and has meningeal signs and symptoms (e.g., neck stiffness, Kernig and/or Brudzinski signs) or in any child whose history or examination suggests the presence of meningitis or intracranial infection.

Aggregate evidence level: B (overwhelming evidence from observational studies).

Benefits: Meningeal signs and symptoms strongly suggest meningitis, which, if bacterial in etiology, will likely be fatal if left untreated.

Harms/risks/costs: Lumbar puncture is an invasive and often painful procedure and can be costly.

Benefits/harms assessment: Preponderance of benefit over harm.

Value judgments: Observational data and clinical principles were used in making this judgment.

Role of patient preferences: Although parents may not wish to have their child undergo a lumbar puncture, health care providers should explain that if meningitis is not diagnosed and treated, it could be fatal.

Exclusions: None.

Intentional vagueness: None.

Policy level: Strong recommendation.
Simple Febrile Seizure

Key Action Statements from AAP Guidelines:

**Action Statement 1—Lumbar Puncture**

In any infant between 6 and 12 months of age who presents with a seizure and fever, a lumbar puncture is an option when the child is considered deficient in *Haemophilus influenzae* type b (Hib) or *Streptococcus pneumoniae* immunizations (ie, has not received scheduled immunizations as recommended) or when immunization status cannot be determined because of an increased risk of bacterial meningitis.

**Aggregate evidence level:** D (expert opinion, case reports).

**Benefits:** Meningeal signs and symptoms strongly suggest meningitis, which, if bacterial in etiology, will likely be fatal or cause significant long-term disability if left untreated.

**Harms/risks/costs:** Lumbar puncture is an invasive and often painful procedure and can be costly.

**Benefits/harms assessment:** Preponderance of benefit over harm.

**Value judgments:** Data on the incidence of bacterial meningitis from before and after the existence of immunizations against Hib and *S pneumoniae* were used in making this recommendation.

**Role of patient preferences:** Although parents may not wish their child to undergo a lumbar puncture, health care providers should explain that in the absence of complete immunizations, their child may be at risk of having fatal bacterial meningitis.

**Exclusions:** This recommendation applies only to children 6 to 12 months of age. The subcommittee felt that clinicians would recognize symptoms of meningitis in children older than 12 months.

**Intentional vagueness:** None.

**Policy level:** Option.
Simple Febrile Seizure

Key Action Statements from AAP Guidelines:

**Action Statement 1— Lumbar Puncture**

A lumbar puncture is an option in the child who presents with a seizure and fever and is pretreated with antibiotics, because antibiotic treatment can mask the signs and symptoms of meningitis.

Aggregate evidence level: D (reasoning from clinical experience, case series).

Benefits: Antibiotics may mask meningeal signs and symptoms but may be insufficient to eradicate meningitis; a diagnosis of meningitis, if bacterial in etiology, will likely be fatal if left untreated.

Harms/risks/costs: Lumbar puncture is an invasive and often painful procedure and can be costly.

Benefits/harms assessment: Preponderance of benefit over harm.

Value judgments: Clinical experience and case series were used in making this judgment while recognizing that extensive data from studies are lacking.

Role of patient preferences: Although parents may not wish to have their child undergo a lumbar puncture, medical providers should explain that in the presence of pretreatment with antibiotics, the signs and symptoms of meningitis may be masked. Meningitis, if untreated, can be fatal.

Exclusions: None.

Intentional vagueness: Data are insufficient to define the specific treatment duration necessary to mask signs and symptoms. The committee determined that the decision to perform a lumbar puncture will depend on the type and duration of antibiotics administered before the seizure and should be left to the individual clinician.

Policy level: Option.
Simple Febrile Seizure

Key Action Statements from AAP Guidelines:

**Action Statement 2—EEG**

An electroencephalogram (EEG) should not be performed in the evaluation of a neurologically healthy child with a simple febrile seizure.

Aggregate evidence level: B (overwhelming evidence from observational studies).

Benefits: One study showed a possible association with paroxysmal EEGs and a higher rate of afebrile seizures.

Harms/risks/costs: EEGs are costly and may increase parental anxiety.

Benefits/harms assessment: Preponderance of harm over benefit.

Value judgments: Observational data were used for this judgment.

Role of patient preferences: Although an EEG might have limited prognostic utility in this situation, parents should be educated that the study will not alter outcome.

Exclusions: None.

Intentional vagueness: None.

Policy level: Strong recommendation.
Simple Febrile Seizure

Key Action Statements from AAP Guidelines:

**Action Statement 3 – Lab studies**

The following tests should not be performed routinely for the sole purpose of identifying the cause of a simple febrile seizure: measurement of serum electrolytes, calcium, phosphorus, magnesium, or blood glucose or complete blood cell count.

**Aggregate evidence level:** B (overwhelming evidence from observational studies).

Benefits: A complete blood cell count may identify children at risk for bacteremia; however, the incidence of bacteremia in febrile children younger than 24 months is the same with or without febrile seizures.

Harms/risks/costs: Laboratory tests may be invasive and costly and provide no real benefit.

Benefits/harms assessment: Preponderance of harm over benefit.

Value judgments: Observational data were used for this judgment.

Role of patient preferences: Although parents may want blood tests performed to explain the seizure, they should be reassured that blood tests should be directed toward identifying the source of their child’s fever.

Exclusions: None.

Intentional vagueness: None.

**Policy level:** Strong recommendation.
Simple Febrile Seizure

Key Action Statements from AAP Guidelines:

Action Statement 4—MRI

**Neuroimaging should not be performed** in the routine evaluation of the child with a simple febrile seizure.

*Aggregate evidence level: B (overwhelming evidence from observational studies).*

Benefits: Neuroimaging might provide earlier detection of fixed structural lesions, such as dysplasia, or very rarely, abscess or tumor.

Harms/risks/costs: Neuroimaging tests are costly, computed tomography (CT) exposes children to radiation, and MRI may require sedation.

Benefits/harms assessment: Preponderance of **harm over benefit**.

Value judgments: Observational data were used for this judgment.

Role of patient preferences: Although parents may want neuroimaging performed to explain the seizure, they should be reassured that the tests carry risks and will not alter outcome for their child.

Exclusions: None.

Intentional vagueness: None.

**Policy level:** Strong recommendation.
Simple Febrile Seizure

Prognosis?

• No increased risk of mortality, hemiplegia, or mental retardation.
• Risk of recurrent febrile seizure about 33%.
• Risk of epilepsy ”only slightly higher than that of general population”.

• 1% → 2%

• Overall-- “benign events with excellent prognoses”.
Simple Febrile Seizure

Time to find out who was paying attention!

Labs?

Lumbar Puncture?

EEG?

MRI?
Complex Febrile Seizure

Criteria:

- **Longer** than 15 minutes
- **Focal** onset
- **Recurrence** within 24 hours (or duration of febrile illness)

*or history of epilepsy (recurrent nonprovoked seizures)
Complex Febrile Seizure

Febrile seizures affect _____ to _____ percent of all children?

2 to 5%\(^1\)

What percentage of febrile seizures are “complex”?

25 to 30%\(^2\)

What percentage of patients with *simple* febrile seizures develop epilepsy?

2%\(^1\)

What percentage of patients with *complex* febrile seizures develop epilepsy

6-8% with 1 feature of CFS,

17-22% with 2 features,

49% with all 3 features.\(^3\)
Complex Febrile Seizure

So what is the work-up for patients with CFS anyway?

Are there any handy AAP practice guidelines?
Complex Febrile Seizure

Recent survey of 353 pediatric emergency medicine physicians in 10 US hospitals

Methodology:

- Volunteer participation through pediatric emergency medicine physician listserv
- 5 hypothetical cases presented
- Questionnaire regarding work-up, admission, treatment following hypothetical cases

Study revealed:

- 54% would obtain blood tests.
- 62% would obtain urine.
- 34% would perform lumbar puncture.
- 36% would perform neuroimaging.

Conclusion: Significant variability in the work-up of patients with CFS.

Potential problems with this survey?
Complex Febrile Seizure

Recent paper from Patel and Vidaurre from Nationwide Children’s Hospital
-Proposed work-up for patients with complex febrile seizures.
-Published in Journal of Child Neurology. June 2013.5

Anup D. Patel, and Jorge Vidaurre J Child Neurol
2013;28:762-767
Complex Febrile Seizure

- Work-up for recurrent febrile seizure (2 or more generalized seizures during febrile illness)?
- Work-up for prolonged (>15 minute) generalized febrile seizure?
- Work-up for focal onset febrile seizure?
- Work-up for any 2 of the 3?
- Work-up for all 3?
4- Epilepsy Syndromes

“...a complex of signs and symptoms that define a unique epileptic condition...” (ILAE)

Patients with similar:
- age of onset
- seizure type(s)
- progression of seizures
- EEG findings
- developmental comorbidities
- genetic changes
- pathophysiologic mechanisms
- response to treatment
4- Epilepsy Syndromes

Why important diagnose specific epilepsy syndrome?

- Guidance in treatment
- Surveillance for comorbidities
- Long-term prognostic information
- Genetic information (recurrence risk)
Generalized (Genetic) Epilepsy Febrile Seizures Plus (GEFS+):

- Primary generalized epilepsy syndrome characterized by both febrile and afebrile seizures.
- AD condition with incomplete penetrance (60-80%) and genetic heterogeneity.
- Prior to onset of afebrile seizures, GEFS+ difficult to distinguish from febrile seizures, detailed family history helps distinguish.
- Multiple genes linked including SCN1A (sodium channel).
  - 90+ different mutations leading to hyperexcitation or hypoexcitation of channel.
  - Other genes include SCN1B, GABRG2 (GABA receptor gamma subunit), PCDH19 (calcium channel).
- Prognosis is generally good—spontaneous remission of seizures by age 11 years in many.
  - Up to 30% have more prolonged and severe epilepsy.
Is GEFS+ a real entity?

“GEFS+” more accurately is a spectrum of fever-associated infantile and childhood epilepsy syndromes.

GEFS+ conditions range from more benign conditions (febrile seizures) to more malignant syndromes such as:

- Severe myoclonic epilepsy of infancy (SMEI)
  - AKA Dravet Syndrome
- Borderline SMEI (SMEB)
- Intractable epilepsy of childhood (IEC)
Dravet Syndrome (severe myoclonic epilepsy of infancy)

Onset in first year of life in a previously well child. Often begin with febrile seizure (febrile status epilepticus not uncommon). Seizures can be generalized or focal onset. Triggered by fever, infection, vaccination, bath. Progression to recurrent, prolonged, and focal seizures.

Diagnosis is clinical, but genetic testing supportive. ~80% of cases have mutation in SCN1A gene, majority represent sporadic mutation. Treatment-- Valproic acid +/- clobazam or stiripentol. Good response to ketogenic diet.

Prognosis is poor:
- Seizures are refractory to treatment.
- Developmental stagnation and regression occurs.
- Mortality rate 16 to 18%, due to status epilepticus, SUDEP, drowning.
Dravet Syndrome

SCN1A mutation present in 80% patients with Dravet syndrome.

Hartmann et al (Epilepsia, March 2015):

- 36 patients with “SCN1A-negative fever-associated syndromic epilepsy”.
  - Genome-wide screening for copy number variations (CNVs) done.
  - Comparative genomic hybridization (CGH) or chromosomal microarray (CMA).
  - 13 rare CNVs identified in 8 of the 36 patients (22%).
    - 4 known pathogenic CNVs:
      - 1q21.1 duplication (Dravet), 14q23.3 deletion (GEFS+), 16p11.2 and 1q44 deletion (fever-associated epilepsy with ASD or ID).
    - 3 likely pathogenic CNVs:
      - 3q13.11 duplication (GEFS+), two de novo duplications at 7p14.2 and 18q12.2 (atypical Dravet).
    - 6 CNVs of unknown significance.
Case 3-7
A 7-month-old girl presented with three bouts of status epilepticus. Her first seizure occurred at 4 months, within 24 hours of an immunization. She had twitching of her left face and arm, which progressed to become secondarily generalized and lasted 45 minutes. Her second prolonged seizure was similar and occurred at 6 months during a viral upper respiratory infection. The third occurred during a car ride on a warm summer day and began with right-sided arm and leg twitching, which secondarily generalized and lasted 65 minutes. Her electrolytes, glucose, calcium, metabolic studies, and MRI were normal, and the EEG showed some mild postictal slowing. Her mother had experienced two simple febrile convulsions in infancy. Genetic testing for SCN1A showed a frameshift mutation. She continued to have bouts of status epilepticus every 2 to 3 weeks despite valproic acid and clonazepam and ultimately striplentol was started, which reduced her bouts of status epilepticus to less than every 6 months. At 24 months, she was clearly delayed with only two words and had some nondisabling myoclonus. Her EEG showed some activation with photic stimulation (Figure 3-8). At 3½ years of age, she was found face down in the bathtub and could not be resuscitated.

Comment. The history of recurrent bouts of focal-onset prolonged seizures in the first year of life, often triggered by fever, should suggest a diagnosis of Dravet syndrome. This is a clinical diagnosis, although approximately 80% of patients are shown to have mutations in the SCN1A gene. Striplentol, when used in combination with clobazam and valproate, may significantly reduce seizure frequency and duration. The initial EEG may be unremarkable. However, a significant proportion of children will show abnormalities with photic stimulation after 2 years of age. Unfortunately, the mortality rate is significant in this syndrome.

**Figure 3-8** Electroencephalograph of a 2-year-old child with Dravet syndrome showing a small amount of generalized spike-wave induced by photic stimulation.
Classification of epileptic syndromes.

**Idiopathic**
- Generalized
  - Infantile onset:
    - Benign neonatal convulsions
    - Benign neonatal familial convulsions
    - Benign myoclonic epilepsy
  - Childhood onset:
    - Childhood absence epilepsy
    - Myoclonic astatic epilepsy
    - Epilepsy with myoclonic absences
    - Generalized epilepsy with febrile seizures plus
  - Adolescent onset:
    - Juvenile myoclonic epilepsy
    - Juvenile absence epilepsy
    - Epilepsy with grand mal on awakening

**Symptomatic**
- Localization-related
  - Infantile onset:
    - Benign partial epilepsy in infancy
    - Benign infanlile familial convulsions
  - Childhood onset:
    - Benign occipital epilepsy—early onset
    - Benign childhood epilepsy with centrotemporal spikes
    - Benign occipital epilepsy—late onset
    - Autosomal dominant frontal lobe epilepsy
    - Familial temporal lobe epilepsy

**Infantile onset:**
- Early myoclonic encephalopathy
- Early infantile epileptic encephalopathy
- Malignant migrating partial seizures
- West syndrome
- Dravet syndrome

**Childhood onset:**
- Lennox-Gastaut syndrome
- Landau-Kleffner syndrome
- Continuous spike-wave in sleep
- Rasmussen encephalitis
- Devastating encephalopathy in school-aged children

**Varying ages:**
- Progressive myoclonic epilepsy

(From 2010 Continuum)
Benign Neonatal Convulsions

**Benign Familial Neonatal Seizures (BFNS)**
- Seizures present during first few weeks of life.
- Brief, but occur 20-30 times per day.
- Normal interictal neurologic exam.
- Family history of similar neonatal seizures.
- AD disorder with 85% penetrance.
- Voltage-gated potassium channels $\text{KCNQ2}$ and $\text{KCNQ3}$ on chromosomes 20q and 8q respectively.
- Favorable outcome with resolution of seizures in infancy and normal neurodevelopment.
- However, up to 8-16% will later develop epilepsy as adults.

**Benign idiopathic neonatal seizures (BINS)**
- Onset of seizures on fifth day of life ("fifth day fits").
- Otherwise healthy, neurologically appropriate, term neonates.
- Partial clonic seizures, may increase in frequency, and culminate in status epilepticus.
- No specific EEG features.
- No family history of neonatal seizures.
- Favorable prognosis as seizures typically resolve after 24 hours.
- Unlike BFNS, there is no increased risk of seizure recurrence in patients with BINS.
Case 3-1
A healthy, term, 2-week old boy presented to the emergency department with frequent seizures. In between the seizures the infant was alert, interactive, and continued to feed vigorously. A sepsis evaluation was negative. His MRI and EEG (Figure 3-2) were also normal. In spite of this, the baby had many seizures per day that did not respond to multiple antiseizure medications. His grandmother then visited the baby and informed his parents that his father, paternal aunt, and cousin all had similar seizures and went on to have normal growth and development.

Comment. BFNS present during the neonatal period in previously healthy term infants. No specific features of the EEG help with the diagnosis. The diagnosis is frequently made when the evaluation for seizures fails to reveal an etiology and there is a family history of neonatal seizures with subsequent normal growth and development. BFNS is an autosomal dominant disorder with 85% penetrance.

Figure 3-2
Normal drowsy interictal electroencephalograph in a neonate with benign familial neonatal seizures.
Myoclonic Astatic Epilepsy (MAE)  
“Doose Syndrome”

Idiopathic (genetic) generalized seizure disorder.  
Up to 32% of children with MAE have family history of epilepsy, inheritance pattern unknown.  
◦ Gene(s) have not yet been implicated.  
Rare, occurs 1:10,000 previously neurodevelopmentally healthy preschool-aged children.  
Multiple seizure types including GTC, myoclonic, absence, myoclonic astatic.  
◦ Similar to seizure types seen in patients with Lennox-Gastaut syndrome (LGS).  
◦ Distinguish from LGS based on observation of myoclonic astatic seizures and with EEG.  
  ◦ Interictal EEG of LGS demonstrates 1.5-Hz to 2.5-Hz generalized slow spike/wave discharges.  
  ◦ EEG of MAE demonstrates 2-Hz to 3-Hz spike/wave discharges.  
Neurodevelopmental arrest is common and regression often occurs.  
Seizures are often difficult to control despite multiple AEDs.  
Ketogenic diet is frequently used with good results.  
Prognosis is variable-- from complete remission to intractable epilepsy with poor cognitive outcome.  
◦ Prognosis is generally more favorable than LGS.
Case 3-2
A previously well 3-year-old boy presented with a history of two generalized tonic-clonic seizures over 4 days. His EEG was normal, and treatment with oxcarbazepine was started. Two weeks later, he had a cluster of 14 generalized tonic-clonic seizures lasting up to 5 minutes each over a 3-day period. He was admitted to the hospital. Oxcarbazepine was stopped, and valproate was loaded with improvement. Over the next 2 weeks, he developed a new seizure type during which he would jerk forward and fall to the ground. Despite increasing doses of valproate, he continued to have both myoclonic astatic as well as generalized tonic-clonic seizures. His EEG now showed slow spike-wave and some high-amplitude slow waves, and several seizures were recorded (Figure 3-3). Clonazepam was added with a marked deterioration in his behavior. He was started on the ketogenic diet with marked improvement of his clinical seizures (Video Segment 3).

Comment. MAE presents acutely in previously well children. Initial seizure types are often generalized tonic-clonic; however, the characteristic myoclonic astatic seizure follows shortly. In distinction to LGS, children with MAE have myoclonic astatic rather than atonic seizures, rare or no tonic seizures, normal development preceding seizure onset, lack of fast frontal or generalized polyspike activity in sleep, presence of parietal theta rhythms, and a higher likelihood of photosensitivity on EEG. Although therapeutic strategies are similar for the two disorders, MAE has a more favorable prognosis.
Childhood Absence Epilepsy (CAE)

Onset between 4 and 10 years in neurodevelopmentally healthy children.

Abrupt onset of impaired consciousness and unresponsiveness.

Seizures last ~10 seconds, can occur up to hundreds of times per day.

Provoked by hyperventilation in 90% of patients.

EEG shows generalized 3-Hz spike/wave discharges.

Generally self-limiting with remission of seizures 2-4 years after onset.

- However, seizures persist into adolescence and adulthood in 12 to 32% of cases.
- 40% of these patients will have GTC seizures as well.

11 to 18% of patients with CAE will develop Juvenile Myoclonic Epilepsy (JME).

CAE is likely AD inheritance with incomplete penetrance. Chromosomes implicated 20q, 16p13.3, 8q24.3.

Treatment— ethosuximide, valproic acid, lamotrigine. Avoid carbamazepine, oxcarbazepine, phenytoin.
Case 3-3
A 6-year-old girl with normal growth and development was brought to her pediatrician for evaluation of spells. Her teachers at school were concerned because she frequently appeared to “stare off” throughout the day. She was missing questions on spelling tests and said she did not remember hearing the questions. Her parents had also noticed episodes during which she appeared to “freeze” briefly, and then returned to normal. Her pediatrician was able to elicit one of these events by asking her to hyperventilate. Her mother had a history of similar seizures. The child was treated with carbamazepine for complex partial seizures. However, her spells dramatically increased in frequency, and she was referred to the neurology department. Her EEG demonstrated frequent 3-Hz spike-and-wave discharges, as well as frequent absence seizures (Figure 3-4). The carbamazepine was discontinued, and she was treated with ethosuximide. Her seizures resolved. By age 10, ethosuximide was discontinued and she remained seizure free (Video Segment 1).

Comment. Frequent, brief seizures without postictal symptoms are typical of absence seizures. Seizures can be provoked with hyperventilation in 90% of children with CAE. Most children have remission of their epilepsy within 2 to 6 years of onset. Medications such as phenytoin, carbamazepine, and oxcarbazepine should be avoided because they are ineffective and may precipitate absence status epilepticus.

FIGURE 3-4 Generalized 3-Hz spike-and-wave discharge during a typical absence seizure.
Juvenile Absence Epilepsy (JAE)

Similar to CAE, but onset generally older than 10 years.

Seizures are longer in duration and less frequent than CAE.

JAE patients are more likely to have GTC seizures.

Interictal EEG in JAE shows 3.5-Hz to 4.0-Hz spike and polyspike/wave discharges.

JAE also is generally responsive to AEDs, but is more likely to be life-long syndrome.
Juvenile Myoclonic Epilepsy (JME)

Onset of seizures between 12 and 18 years in neurodevelopmentally healthy adolescents. Seizure types include absence, myoclonic, generalized tonic-clonic. First seizure type noted is often GTC, provoked by sleep deprivation. History may reveal “staring spells” and myoclonic jerks in the early morning. Routine EEG abnormal in 50 to 75%.

- 4-Hz to 6-Hz generalized atypical spike and polyspike/wave discharges.
- Focal discharges seen in up to 30% of patients.

Photosensitivity common, may provoke myoclonic seizure. Provoking factors include sleep deprivation, alcohol consumption, menstruation. Inheritance is complex--

- classic form is AD and linked to chromosome 6p12-11.
- patients with primarily absence seizures linked to chromosomes 15q14 or 6p21.3.
- 2q22-23 and 5q34-34 also linked to JME.

Treatment with valproic acid, levetiracetam, lamotrigine, topiramate, zonisamide.

- Avoid carbamazepine, phenytoin, gabapentin-- these make myoclonic seizures worse!

Prognosis generally good but often lifelong syndrome.
Case 3-4
A 16-year-old previously healthy boy had a generalized tonic-clonic seizure while on vacation with his family. In the emergency department he had a second generalized tonic-clonic seizure. His family acknowledged he had been staying up later than usual because of the vacation. His family also noticed that he frequently dropped his breakfast dishes. As the vacation week progressed, he seemed to be spilling things more frequently. He had had similar myoclonic jerks immediately preceding his generalized tonic-clonic seizure. EEG demonstrated 4 Hz to 6 Hz generalized atypical spike-and-wave discharges and photosensitivity (Figure 3-5). He was treated with valproic acid and became seizure free for the next 5 years. He then discontinued valproic acid because of seizure freedom but had recurrence of myoclonic and generalized tonic-clonic seizures shortly thereafter. Valproic acid was restarted but at a lower dose. He remained free of generalized tonic-clonic seizures but had rare myoclonic seizures after sleep deprivation or alcohol consumption. Video Segment 2 depicts a cluster of myoclonic seizures during photic stimulation.

Comment. Children with JME frequently come to medical attention after generalized tonic-clonic seizures. A history of preceding myoclonic and absence seizures must be sought. Valproic acid is the traditional treatment for JME, with an excellent response. However, only 10% of children are able to remain seizure free after discontinuing antiseizure medications.

Figure 3-5. Interictal generalized atypical spike-and-wave discharge in an adolescent with juvenile myoclonic epilepsy.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Age at Onset</th>
<th>Clinical</th>
<th>EEG</th>
<th>Genetics</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign neonatal convulsions</td>
<td>Day 1 to 7, peak day % of life</td>
<td>Partial clonic, may migrate Apnea Rare tonic Many progress to status epilepticus</td>
<td>Normal; excessively discontiguous, focal or multifocal discharges</td>
<td>Idiopathic</td>
<td>Phenobarbital, Fosphenytoin Benzodiazepines</td>
<td>Excellent, rare recurrence of seizures</td>
</tr>
<tr>
<td>Benign neonatal familial convulsions (BNFC)</td>
<td>Majority during neonatal period, typically during first week of life</td>
<td>Tonic-clonic Apnea Autonomic phenomena Normal behavior interictally</td>
<td>May be normal or show transient changes, including focal epileptiform discharges</td>
<td>Autosomal dominant, 85% penetrance BFNC1 due to mutation in KCNQ2 on 2q13.3, BFNC2 due to mutation in KCNQ1 on 8q24</td>
<td>Seizures usually remit by midinfancy 10% to 16% will later develop epilepsy</td>
<td></td>
</tr>
<tr>
<td>Benign myoclonic epilepsy</td>
<td>4 months to 3 years</td>
<td>Myoclonic seizures Absences Rare GTC</td>
<td>Unknown, but 31% have a family history</td>
<td>Valproate</td>
<td>Excellent</td>
<td></td>
</tr>
<tr>
<td>Generalized epilepsy with febrile seizures plus</td>
<td>Infancy to adolescence beyond age 6 years and afebrile myoclonic, atonic, tonic-clonic, absence, and complex partial seizures</td>
<td>Febrile seizures beyond age 6 years and afebrile myoclonic, atonic, tonic-clonic, absence, and complex partial seizures</td>
<td>Autosomal dominant, up to 80% penetrance, linked to multiple chromosomes: SCN1A on 19q13, SCN1B on 2q24, and GABRB3 on 5q33-q34</td>
<td>Valproate, ethosuximide, benzodiazepines</td>
<td>Variable; most do well, but up to 20% may have more severe epilepsy</td>
<td></td>
</tr>
<tr>
<td>Myoclonic atactic epilepsy</td>
<td>7 months to 8 years, peak 2 to 6 years</td>
<td>Myoclonic Atonic atactic Myoclonic atactic Absences Tonic</td>
<td>Normal at onset Later, slowing of the background and 2-Hz to 3-Hz generalized irregular spike-and-wave discharges</td>
<td>Family history of seizures in 32%</td>
<td>May be favorable in 50% to 89%, although up to 41% may have borderline IQ or mental handicap, and some will develop intractable epilepsy</td>
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<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Age at Onset</th>
<th>Clinical</th>
<th>EEG</th>
<th>Genetics</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood absence epilepsy</td>
<td>2 to 12 years</td>
<td>More common in girls</td>
<td>Normal background with 3-Hz generalized spike-wave discharges</td>
<td>Possibly autosomal dominant, linked to 20q and 8q43</td>
<td>Ethosuximide</td>
<td>Valproate</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Eyelid myoclonia with and without absences</td>
<td>2 to 14 years, peak 6 to 8 years</td>
<td>Myoclonia of eyelids, upward deviation of eyes, and retropulsion of the head with or without impairment of consciousness, mainly after eye closure</td>
<td>Frequent high-amplitude 3-Hz to 6-Hz generalized spike- and polyspike- and-wave discharges, typically seen with eye closure</td>
<td>Unknown, but must have a family history of epilepsy</td>
<td>Valproate, ethosuximide, clonazepam, possibly levetiracetam</td>
<td></td>
<td>Myoclonia is resistant to treatment and the syndrome is lifelong, even in those with well-controlled seizures</td>
</tr>
<tr>
<td>Perioral myoclonia with absences</td>
<td>2 to 13 years, median 10 years</td>
<td>Absence with ictal perioral myoclonia</td>
<td>Bursts of 4-Hz to 7-Hz generalized, but often asymmetric, spike- and polyspike-wave, may have focal discharges, ictal EEG 3-Hz to 4-Hz irregular generalized spike- and polyspike- and-wave discharges</td>
<td>Unknown, but 50% have a first-degree relative with idiopathic generalized epilepsy and absences</td>
<td>Valproate alone or with ethosuximide, lamotrigine, clonazepam, lamotrigine, valproate</td>
<td>Lamotrigine</td>
<td>Usually resistant to medication and may be lifelong</td>
</tr>
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<table>
<thead>
<tr>
<th>Age at Syndrome Onset</th>
<th>Clinical</th>
<th>EEG</th>
<th>Genetics</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>11 months to 12 years, mean 7 years</td>
<td>Myoclonic absence seizures</td>
<td>Generalized 3 Hz with a strict correlation between EEG discharge and myoclonia</td>
<td>20% have a family history of epilepsy</td>
<td>Valproate with ethosuximide</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>Absence seizures in childhood</td>
<td>Myoclonus early adolescence</td>
<td>Normal background with 3-Hz to 4-Hz, generalized spike-and-wave discharges</td>
<td>Complex inheritance linked to 6p, 18q, 15q14, and 8q23.3-q24.1</td>
<td>Valproate</td>
</tr>
<tr>
<td>Juvenile absence epilepsy</td>
<td>Adolescence</td>
<td>Daily brief absence seizures</td>
<td>Normal background with 3-Hz to 4-Hz, generalized spike-and-wave discharges</td>
<td>Possible localization to 21q22.1</td>
<td>Valproate</td>
</tr>
<tr>
<td>Epilepsy with grand mal on awakening</td>
<td>Seizures occur shortly after waking up, may be associated with absence or myoclonic seizures</td>
<td>Slow background, generalized spike-and-wave discharges, photosensitivity</td>
<td>Thought to be genetic; 3.3% have a first-degree relative with epilepsy</td>
<td>Response to AED is good, but relapse occurs with AED discontinuation and sleep deprivation</td>
<td></td>
</tr>
</tbody>
</table>

EEG = electroencephalograph; GTC = generalized tonic-clonic; AED = antiepileptic drug.
Benign Occipital Epilepsy, early

**Early-onset** benign childhood epilepsy with occipital paroxysms

“Panayiotopoulos Syndrome” (PS)

Most commonly in preschool-aged children but can occur anytime between 1 and 14 years of age.

Seizures consist of **autonomic** symptoms including nausea, emesis, retching, pallor, urinary incontinence, hypersalivation. Consciousness is preserved.

Seizure can progress to gaze deviation, speech arrest, convulsive activity, with associated loss of awareness.

Autonomic symptoms can be prolonged-- “autonomic status epilepticus”.

Interictal EEG shows multifocal, high-amplitude epileptiform discharges. May also have **occipital epileptiform discharges**, which are suppressed with eye opening.

Initially may be difficult to treat, but **spontaneous remission** occurs within 1-2 years in 90% of patients.
Late-onset childhood epilepsy with occipital paroxysms
   “Idiopathic childhood occipital epilepsy of Gastaut”

Occurs in school-aged children (as opposed to preschool-aged children with early-onset).

Visual hallucinations followed by gaze deviation, ipsilateral head deviation, possible secondary generalization.

Awareness is maintained until gaze deviation occurs.

Ictal and post-ictal headache are common.

EEG is similar to that of early-onset benign occipital epilepsy (PS).

Remission occurs in only 50-60% within 2-4 years.

Treatment with carbamazepine.
Benign Childhood Epilepsy With Centrotemporal Spikes (BCECTS)

“Benign Rolandic Epilepsy”

Most common idiopathic partial epilepsy.

Onset between 4-10 years.

Nocturnal seizures consisting of perioral paresthesias, ipsilateral facial myoclonus, salivation, speech arrest, guttural noises.

Seizure may spread to include ipsilateral or generalized convulsions.

EEG shows high-amplitude centrotemporal spikes, activation during sleep.

Likely AD inheritance with incomplete penetrance.
  ◦ involvement of chromosomes 1q and 15q14.

Typically easily controlled with AEDs. Medication may not be necessary.

Spontaneous remission by age 17 years or earlier.
Case 3-5
A 10-year-old healthy boy had been on vacation with his family. While sharing a hotel room, his family was awakened by the boy sitting up and making strange sounds. He was noted to have salivation and twitching of the right side of his face that seemed to spread to his right arm. Shortly thereafter, he returned to baseline. Six months later, he had a similar event. However, this seizure was longer and progressed to a generalized tonic-clonic seizure. His EEG demonstrated spikes over the bilateral centrottemporal head regions with increased activation during sleep (Figure 3-6). His parents declined treatment for their son because his older brother had similar seizures that he outgrew.

Comment. BCECTS presents with nocturnal partial seizures involving the rolandic area, the lower face, and occasionally the hand. The seizures are typically brief but may secondarily generalize. BCECTS is likely inherited through a complicated inheritance pattern. Children with BCECTS usually have infrequent seizures that are predominantly nocturnal. Therefore, medication may not be indicated.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Age at Onset</th>
<th>Clinical</th>
<th>EEG</th>
<th>Genetics</th>
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<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign infantile familial convulsions</td>
<td>3.5 to 12.0 months</td>
<td>Psychomotor arrest, eye deviation, cyanosis, limb jerks in clusters of 5 to 10 per day, with or without secondary generalization</td>
<td>Normal or show occipitoparietal spike and wave; ictal focal discharge with spread</td>
<td>Heterogeneous genetics possibly linked to 19q11-q13 and 16p12-q12, with 76% penetrance</td>
<td>If necessary, carbamazepine, phenobarbital, valproate, zonisamide</td>
<td>Excellent; seizures resolve without recurrence and development is typically normal</td>
</tr>
<tr>
<td>Benign partial epilepsy in infancy</td>
<td>3 to 20 months, mean 9.5 months</td>
<td>Seizure spreading, loss of consciousness, febrile seizures, or benign infantile familial convulsions</td>
<td>Normal interictally, ictal focal low-voltage fast or sharp waves, with or without theta waves secondary generalization</td>
<td>Family history of febrile, febrile seizures, or benign infantile familial convulsions present in up to 55%</td>
<td>If necessary, carbamazepine or phenobarbital</td>
<td>Seizures resolve by 2 to 3 years of age, normal development</td>
</tr>
<tr>
<td>Childhood epilepsy with occipital paroxysms—early onset</td>
<td>1 to 14 years, typically 3 to 6 years</td>
<td>Ictal autonomic symptoms including nausea, vomiting, pallor, tachycardia, followed by confusion</td>
<td>Multifocal, high amplitude, sharp waves, maximal occipital</td>
<td>Probably genetic; reported seizures similar to idiopathic, benign childhood epilepsy with centrotemporal spikes</td>
<td>Most do not require antiseizure medication treatment</td>
<td>Excellent; most have infrequent seizures that resolve in 1 to 2 years, risk of adult epilepsy is the same as the general population</td>
</tr>
<tr>
<td>Benign childhood epilepsy with centrotemporal spikes</td>
<td>1 to 14 years, typically 7 to 10 years</td>
<td>Hemifacial sensorimotor seizure with spread to ipsilateral hand, progression to homolateral or generalized tonic-clonic in 50%</td>
<td>Centrotemporal spikes activated by drowsiness and sleep</td>
<td>Possibly linked to 15q14; EEG findings are autosomal dominant with age-dependent penetrance</td>
<td>Most do not require antiseizure medication treatment</td>
<td>Excellent; most resolve before age 16 years</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Syndrome</th>
<th>Age at Onset</th>
<th>Clinical Features</th>
<th>EEG</th>
<th>Genetics</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood epilepsy with</td>
<td>3 to 15 years</td>
<td>Visual hallucinations, focal blindness,</td>
<td>Occipital spikes, +/-</td>
<td>Rare family history of same seizure type, but family history of epilepsy</td>
<td>&gt;90% respond to</td>
<td>50% to 60% resolve in 2 to 4 years, remainders continue to have visual and infrequent generalized tonic-clonic seizures</td>
</tr>
<tr>
<td>occipital paroxysms—late onset</td>
<td>typically 8 to 11 years</td>
<td>generalizes, then eye deviation, loss of awareness and convulsive activity</td>
<td>postictal headache</td>
<td>and migraine is increased</td>
<td>carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant frontal lobe epilepsy</td>
<td>Mean age of onset 11 years</td>
<td>Seizures while falling asleep or awakening: aura of fear, shivering, then hyperkinesis in clusters with or without loss of consciousness</td>
<td>Normal or frontal spikes</td>
<td>Autosomal dominant, 70% penetrance, related to CHRMA4 on 20q13.2, CHRN2 on 1p21, and other nicotinic acetylcholine receptor genes on 15q</td>
<td>Carbamazepine</td>
<td>Usually respond well to antiseizure medications</td>
</tr>
<tr>
<td>Familial temporal lobe epilepsy</td>
<td>Second or third decade</td>
<td>Lateral: simple partial seizures with acoustic and visual hallucinations, some secondarily generalize Mesial: autonomic aura, déjà vu, then complex partial seizure</td>
<td>Epileptiform activity over temporal areas</td>
<td>Autosomal dominant, some linked to 10q22-q24</td>
<td>Carbamazepine</td>
<td>Most respond well to antiseizure medications</td>
</tr>
</tbody>
</table>
West Syndrome

Triad of infantile spasms, hypsarrhythmia, psychomotor delay.

Affects 1 per 1900 to 3900 infants. Most common epileptic encephalopathy.

Peak age of onset is 4 to 8 months.

Semiology of spasms:
- Transient contraction of trunk, neck, extremities, followed by brief tonic component.
- Flexor, extensor, or mixed.
- Several clusters per day.
- Asymmetric spasms suggest focal cortical lesion.

Characteristic EEG finding of hypsarrhythmia—disorganized, slow, high-voltage multifocal epileptiform discharges.

Etiologies include malformations of cortical development, neurocutaneous disorders (TS), inborn errors of metabolism, mitochondrial disease, ischemia, infection, trauma.

Psychomotor delay and developmental regression are common.

Treatment—steroids, corticotropin (ACTH), vigabatrin (especially in TS patients), valproic acid, topiramate, levetiracetam.
Case 3-6
A previously healthy 7-month-old infant girl presented with recurrent clusters of spells during which she suddenly flexed at the trunk and neck and extended her arms. Over the past month, her spells had become more frequent and she was no longer rolling over or laughing like she could previously (Video Segment 7).

Comment. This infant is presenting with infantile spasms. Her interictal EEG demonstrates a slow, high-amplitude, poorly organized background with multifocal epileptiform discharges, consistent with hypsarrhythmia (Figure 3-7). In addition, she now has developmental regression and delay. The triad of infantile spasms, hypsarrhythmia, and developmental delay are consistent with West syndrome. In order to improve developmental outcome, it is important to recognize and treat infantile spasms early.

Figure 3-7 A. Interictal EEG in a child with infantile spasms demonstrating a slow, poorly organized, high-amplitude background with multifocal sharp waves and electrodecrement. Consistent with hypsarrhythmia.

B. Total EEG in a child with infantile spasms demonstrating a high-amplitude generalized sharp wave followed by electrodecrement.
Lennox-Gastaut Syndrome

Triad -- **multiple seizure** types, interictal EEG pattern of diffuse slow spike/wave complexes, cognitive dysfunction.

Onset in preschool years.

Two-thirds have existing brain abnormalities (hypoxic ischemic injury, malformations of cortical development, neurocutaneous disorders, etc.)

1.9 to 2.1 per 100,000 children.

6 to 7% of pediatric intractable epilepsy.

Intractable drop seizures common.

EEG shows 1.5-Hz to 2.5-Hz polyspike and spike/wave discharges on slow background.

Medically refractive

**Ketogenic diet**, vagal nerve stimulation (VNS), corpus callostopmy.
Rasmussen Encephalitis

Intractable focal epilepsy.

Progressive atrophy in affected hemisphere.

Seizures are refractory to multiple AEDs.

HEMISPHERECTOMY!
Case 3-9
A 4-year-old girl presented with a 3-year history of focal seizures that started with rhythmic twitching of her left arm, followed by left face. At times, they were associated with loss of awareness, and they were rarely secondarily generalized. Over time, seizures increased in frequency and duration to the point they were occurring multiple times per day. She had gradual onset of a left hemiparesis over the past 2 months. On examination, she was noted to have arrhythmic twitching of her left hand and face. Seizures had persisted despite treatment with five antiepileptic drugs (Video Segment 6).

Comment. This young girl had epilepsy partialis continua of her left hand and face. Her history of progressive seizures and hemiparesis is suggestive of Rasmussen encephalitis. Her MRI showed right hemispheric atrophy (Figure 3-10), which had not been present 18 months earlier. This condition is notoriously resistant to antiepileptic drugs. While immunotherapy may result in transient response, most children ultimately require hemispherectomy. This girl underwent hemispherectomy 2 months after video was obtained and has remained seizure free.

**Figure 3-10**
A, Ictal EEG in a child with Rasmussen encephalitis with a focal motor seizure, demonstrating rhythmic muscle artifact that corresponded with frequency of hemifacial clonic seizure, but no EEG correlate. B, MRI (coronal T1) demonstrates right hemispheric atrophy.
Epilepsy secondary to a structural cause. A, Serial T2-weighted brain MRI showing changes over time in untreated Rasmussen syndrome. Earliest abnormal MRI at 3 years 2 months of age during the acute phase shows increased cortical signal (arrows). B, C, MRIs at 13 years 9 months in the residual phase show severe unilateral atrophy of the entire right hemisphere with normal signal intensity. D, Brain MRI of a 10-year-old girl with pharmaco-resistant epilepsy with gelastic seizures secondary to hypothalamic hamartoma. This is a T2 fast-spin echo, coronal view, and E, postcontrast T1 inversion-recovery fast-spin gradient echo, sagittal view, showing a lesion centered in the left aspect of the hypothalamus and extending into the third ventricle (arrow). F, Brain MRI performed on a 3-Tesla scanner for presurgical evaluation of an 11-year-old boy with pharmaco-resistant epilepsy with focal seizures arising from the left temporal lobe. This is a T2 fast-spin echo, coronal view, showing asymmetrical volume of the left medial temporal lobe with hyperintensity and obscuration of the hippocampal internal architecture (arrow).

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Age at Onset</th>
<th>Clinical</th>
<th>EEG</th>
<th>Etiology</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early myoclonic encephalopathy</td>
<td>Birth to first few weeks</td>
<td>Prominent fragmentary myoclonus, Partial seizures with eye deviation and autonomic signs, Tonic spasms may develop later, Hypoactive, hypotonic infant</td>
<td>Suppression burst without EEG correlating to myoclonus</td>
<td>Mostly unknown, Metabolic disorder is rarely found</td>
<td>No effective therapies</td>
<td>Very poor; high mortality in first few years of life</td>
</tr>
<tr>
<td>Early infantile epileptic encephalopathy</td>
<td>First few weeks to months</td>
<td>Tonic spasms, Partial seizures</td>
<td>Suppression burst</td>
<td>Malformation of cortical development, Some unknown</td>
<td>Vigabatrin, zonisamide, or corticotropin may be helpful, many intractable to AEDs, Epilepsy surgery if focal malformation present</td>
<td>Poor</td>
</tr>
<tr>
<td>Malignant migrating partial seizures in infancy</td>
<td>First 7 months</td>
<td>Focal motor seizures often with apnea, cyanosis, flushing, Often cluster, May become secondarily generalized with increasing age</td>
<td>Slow background and multifocal discharge, Ictal spikes</td>
<td>Unknown</td>
<td>Usually intractable to AEDs, Bromides or stiripentol and clonazepam may rarely help</td>
<td>Very poor</td>
</tr>
<tr>
<td>West syndrome</td>
<td>Peak 4 to 7 months</td>
<td>Epileptic spasms in clusters, most commonly on awakening, Hypersynchrony Multiple—see text</td>
<td></td>
<td></td>
<td>First line: corticotropin, steroid, or vigabatrin, Second line: valproate, topiramate, benzodiazepines, ketogenic diet</td>
<td>Often poor but depends on etiology</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Age at Onset</td>
<td>Clinical Features</td>
<td>EEG Features</td>
<td>Etiology</td>
<td>Treatment / Prognosis</td>
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<tr>
<td>Dravet syndrome</td>
<td>First year of life</td>
<td>Recurrent, prolonged focal or generalized tonic-clonic seizures, often triggered by fever, infection, immunization, or bathing</td>
<td>Often normal initially. Later, slow background, multifocal or generalized polyspike-wave discharge</td>
<td>JCN A gene mutation on chromosome 2</td>
<td>First line: Valproate and clobazam with briviact added if these are not effective, ketogenic diet. Second line: Topiramate, levetiracetam, zonisamide. Often poor Mortality 16% to 18%—50% DEP, status, drowning.</td>
<td></td>
</tr>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>2 to 8 years, peak 3 to 5 years</td>
<td>Multiple types of generalized seizures including tonic, atonic, atypical absence, myoclonic, developmental delay. Most children have preexisting neurologic disability</td>
<td>Frontally predominant slow spike in sleep, use fast, frontally predominant 10-Hz rhythmic spike activity</td>
<td>Multiple</td>
<td>Early use of the ketogenic diet should be considered First line: AEDs: valproate, levetiracetam, topiramate. Seizures often refractory Mental handicap in 80%.</td>
<td></td>
</tr>
<tr>
<td>Landau-Kleffner syndrome</td>
<td>3 to 8 years</td>
<td>Acquired auditory agnosia Three-fourths have seizures—partial motor.seizures affecting lower face and upper extremity most common</td>
<td>Centrotemporal sharp waves. Usually idiopathic that markedly increase in sleep</td>
<td>Usually idiopathic</td>
<td>Oral steroids, high-dose diazepam EE changes and seizures resolve in mid to late childhood but children may be left with language impairment</td>
<td></td>
</tr>
<tr>
<td>Continuous spike-wave in sleep</td>
<td>3 to 8 years</td>
<td>More global regression with partial and generalized (atypical absence, atonic, generalized tonic-clonic, but not tonic) seizures.</td>
<td>Frontal and multifocal sharp waves that become nearly continuous in sleep</td>
<td>Often symptomatic of underlying brain insult</td>
<td>Oral steroids or high-dose diazepam EE changes and seizures improve or resolve in mid to late childhood, but children are often left with cognitive impairment</td>
<td></td>
</tr>
<tr>
<td>Syndrome</td>
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<tr>
<td>Rasmussen encephalitis</td>
<td>18 months to young adulthood</td>
<td>Progressively worsening focal seizures, epilepsy partialis continua, progressive hemiparesis and atrophy of affected hemisphere</td>
<td>Hemispheric slowing, multifocal epileptiform discharges are widespread over affected hemisphere and may be bilateral</td>
<td>Immune-mediated but details poorly understood</td>
<td>Immunotherapy can be tried, but most children two-thirds are seizure free; cognitive deterioration stabilizes, but hemiparesis is permanent (although children can ambulate)</td>
<td></td>
</tr>
<tr>
<td>Devastating encephalopathy in school-aged children</td>
<td>4 to 11 years</td>
<td>Intractable convulsive status epilepticus with fever but no intracranial infection that is followed by intractable temporal lobe epilepsy</td>
<td>Recurrent, often multifocal seizures with status epilepticus</td>
<td>Unknown</td>
<td>No effective treatments reported</td>
<td>Very poor; children are left with intractable partial epilepsy and cognitive delay</td>
</tr>
<tr>
<td>Progressive myoclonic epilepsy</td>
<td>Infancy to adulthood</td>
<td>Progressive myoclonus; generalized tonic-clonic and other seizures, mental deterioration, cerebellar dysfunction</td>
<td>Slow background with generalized spike- and polyspike-and-wave discharge</td>
<td>Multiple metabolic and neurodegenerative conditions</td>
<td>AEDs may help but do not provide complete control; valproate, clonazepam, zonisamide, levetiracetam</td>
<td>Progressive but rapidity depends on etiology</td>
</tr>
</tbody>
</table>

EEG = electroencephalograph; AED = antiepileptic drug; SUDEP = sudden unexplained death in epilepsy.
Advanced Epilepsy Panel

Table. Genes Tested in the Epilepsy Advanced Sequencing Evaluation, by Associated Phenotype*

<table>
<thead>
<tr>
<th>Epilepsy Phenotype*</th>
<th>Genes Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized, absence, focal, and myoclonic epilepsies (5001)</td>
<td>ALDH7A1, CACNA1A, CASR, CHRNA2, CHRNA4, CHRNA5, CHTB, DEPDC5, EFHC1, EPHB2, GABRA1, GABRA3, GABRD, GABRG2, GRIN2A, KCNMA1, KCNJQ2, KCNQ3, KCNT1, KCNT2, LGI1, MBD5, ME2, NLRC1, PCDH19, PRKCI, PRKCI2, PRRT2, SCA10, SCN1A, SCN1B, SCN2A, SCN9A, SLC21A, SLC24A10, TBC1D24</td>
</tr>
<tr>
<td>Epileptic encephalopathies (5002)</td>
<td>ARHGEF9, ARX, CDKL5, CNTNAP2, FOXL1, GABRG2, GRIN2A, KCNT1, MECP2, NRXN1, PCDH19, PKP2, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SCN1A, SCN1B, SCN2A, SCN8A, SLC25A22, SLC22A1, SLC9A6, SPTAN1, STXBP1, SYNGAP1, TCF4, TREX1, UBE3A, ZEB2</td>
</tr>
<tr>
<td>Neuronal migration disorders (5003)</td>
<td>ARID2, ARX, COL2A1, COL4A1, CPT2, DCX, EMA, FGF1, FMR1, FYN, GABRA5, IAMS2, LARGE, MAX, PAPA1, PAX6, PHEX, POMT1, POMT2, PQBP1, RAB3GAP1, RELN, SNAPP9, SPLAY2, TUBA1A, TUBA1B, TUBA8B, TUBB2B, WDR62</td>
</tr>
<tr>
<td>Epilepsy in X-linked intellectual disability (5004)</td>
<td>ARHGEF9, ARX, ATP6AP2, ATRX, CASK, CDKL5, CUL4B, DCX, FGFR1, GP3, GRIA3, HS0710, KDM5C, MECP2, OAF, ORPH1, PAK3, PCDH19, PHF6, PIP1, RAB3B, SLC9A6, SMC1A, SMG5, SRPX2, SYN</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis (5005)</td>
<td>CLN3, CLN5, CLN6, CLN8, CLN9, CTSD, DNA1CS, KCTD7, MFS1, PPT1, TPPI</td>
</tr>
<tr>
<td>Epilepsy with migraine (5006)</td>
<td>ATP1A2, CACNA1A, NOTCH3, POLG, PRRT2, SCN1A, SLC21A</td>
</tr>
<tr>
<td>Syndromic disorders (5007)</td>
<td>ATP2A2, ATP6V0A2, CACD1, CLCNKA, CLCNKB, VPS15, KCNA1, KCNJ1, KCNJ10, KIAA1279, LBR, LGI1, MLLE, MIPB, PANK2, SERTP1, PIGV, PLAG2G1, RAI1, SETBP1, SMG3, SYNGAP1, TXN1, TSC1, TSC2, VPS13A</td>
</tr>
<tr>
<td>Infantile spasms (5008)</td>
<td>ARX, CDKL5, FOXL1, GABRG3, GRIN2A, MEF2C, SCN2A, SLC25A22, SPTAN1, STXBP1</td>
</tr>
</tbody>
</table>

* Some genes in this panel are associated with more than 1 epilepsy phenotype.
* Testing for the groups of genes associated with each phenotype may be ordered separately, using the test codes listed in parentheses, for patients whose phenotypes suggest specific syndromes.
References


References cntd.


