Pediatric Epilepsy

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Epidemiology:
Incidence and Prevalence
• 20,000 to 45,000 children diagnosed with epilepsy annually
• As many as 325,000 American children between the ages of 5 and 14 years have active epilepsy
• Some evidence suggests a decline in epilepsy incidence over the last few decades

Etiology of Epilepsy in Children <15 Years of Age


Idiopathic 67.6%
Congenital 20.0%
Trauma 4.7%
Vascular 1.5%
Neoplastic 1.5%
Infection 4.0%
Degenerative 0.7%

Incidence of Seizure Types in Children <15 Years


Absence 13%
Other generalized 11%
Tonic-clonic 19%
Simple partial 11%
Myoclonic 7%
Complex partial 23%
Unknown/multiple 9%
Other partial 7%

Incidence of Seizure Types by Age

Seizure Type vs. Epileptic Syndrome

- A seizure is determined by the patient’s behavior and EEG pattern during the ictal event.
- An epileptic syndrome is defined by:
  - seizure type(s)
  - natural history
  - EEG (ictal and interictal)
  - response to treatment
  - etiology

Seizures and Syndromes: Age of Onset

Age-Related presentations of some common epilepsy syndromes listed with common seizure semiology and interictal EEG findings:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Normal Exam</th>
<th>Abnormal Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td>Benign familial neonatal convulsions; Benign neonatal convulsions (clonic/normal or sharp theta)</td>
<td>Early myoclonic epilepsy (Aicardi’s syndrome); Early infantile epileptogenic encephalopathy; (Ohtahara syndrome) (myoclonus, tonic/burst suppression)</td>
</tr>
<tr>
<td>Pre-School</td>
<td>Myoclonic-astatic (myoclonic-astatic, vibratory tonic/GSW rhythmic theta)</td>
<td>West’s syndrome (spasms/hypsarrhythmia); Severe infantile myoclonic (Dravet syndrome) (Myoclonus, FS, partial/GSW, PPR); Migrating seizures (hypomotor, other/multifocal spikes)</td>
</tr>
</tbody>
</table>

Diagnostic Approach: Seizure Semiology/EEG Finding

<table>
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<tr>
<th>Age Group</th>
<th>Normal Exam</th>
<th>Abnormal Exam</th>
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</thead>
<tbody>
<tr>
<td>Infantile</td>
<td>Benign infantile spasms (Lombroso) (spasms/normal); Benign myoclonic epilepsy (myoclonus/GSW); Benign infantile seizures (various descriptions, normal)</td>
<td>Lennox-Gastaut (tonic seizures, atypical absence, partial/low, ie, 2.5-Hz spike-wave)</td>
</tr>
<tr>
<td>Pre-School</td>
<td>Myoclonic-astatic (myoclonic-astatic, vibratory tonic/GSW rhythmic theta)</td>
<td>Landau-Kleffner, CSWS (rare seizures/continuous spike-waves in sleep); Myoclonic absence (myoclonic absence/3-Hz spike-wave); Epilepsia partialis continua syndromes (Kojewnikoff, Rasmussen) (epilepsia partialis continua/polymorphic spikes)</td>
</tr>
<tr>
<td>School age</td>
<td>Benign Rolandic, benign occipital (sensory, clonic/stereotyped IEDs); Childhood absence (absence/3-Hz spike-wave)</td>
<td>Progressive myoclonus (myoclonus, other/slowed background)</td>
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Diagnostic Approach: Seizure Semiology/EEG Finding

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<th>Age Group</th>
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<th>Abnormal Exam</th>
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</thead>
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<tr>
<td>Juvenile</td>
<td>Juvenile myoclonic; Juvenile absence; GTCS on awakening (as described) generalized fast polyspike-waves, PPR</td>
<td>Progressive myoclonus (myoclonus, other/slowed background)</td>
</tr>
</tbody>
</table>

Diagnostic Approach: Seizure Semiology/EEG Finding

Epidemiology: Seizure Type and Epilepsy Syndrome

- In children, the majority (½ to ⅔) of seizures and epilepsy syndromes are partial-onset.
- This compares with 75% to 90% in adults.

<table>
<thead>
<tr>
<th>Researchers</th>
<th>Patient Sample</th>
<th>n</th>
<th>% Partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sillanpaa et al (Turku, Finland)</td>
<td>Population-based</td>
<td>235</td>
<td>64</td>
</tr>
<tr>
<td>Berg et al (Conn, US)</td>
<td>Community-based</td>
<td>613</td>
<td>59</td>
</tr>
</tbody>
</table>

CSWS = continuous spike-wave during slow-wave sleep; IED = interictal epileptiform discharges
Epidemiology: Natural History and Prognosis

- Median age of seizure onset is 5 to 6 years
- Recurrence risk following first unprovoked seizure ranges from 27% to 76%
- AED therapy following a first unprovoked seizure lowers the recurrence risk by roughly 50%
- The majority of patients with childhood-onset epilepsy attain remission

- 60% to 75% of patients seizure free on AEDs for more than 2 years remain so after AED discontinuation
- Childhood-onset epilepsy is associated with adverse social and educational outcomes
- Childhood-onset epilepsy carries an increased mortality rate

Epidemiology: Patients with Developmental Disabilities (DD)

- Increased seizure risk
- Amplified increased seizure risk if multiple disabilities are present
- Lower age of epilepsy onset than in neurologically normal children
- Increased risk to have multiple seizure type and to develop refractory epilepsy

Diagnostic Approach

- Step 1: Consider age
- Step 2: Assess neurologic functioning
- Step 3: Evaluate seizure semiology and EEG characteristics

Diagnostic Approach: Neurologic Functioning

- Normal
  - Hx: no antecedent event that predisposes to seizure
  - Hx: normal development and cognitive function
  - PE: normal general and neurologic exam
  - Tests: consistent with normal nervous system
- Abnormal
  - substantial delays or focal deficits
  - diffuse encephalopathy or focal process

How Do We Treat Children with Epilepsy?

- Therapeutic value
- Secondary effects
Infantile Spasms

- Onset at 4-8 months of life
- Characterized by clusters of flexor, extensor, or mixed myoclonic jerks
- May have associated autonomic or focal features
- Various etiologies
- Resistant to standard AEDs
- DD/MR frequent
- Mortality 20% by 5 yo

Prevalence of Spasms

Infantile Spasms: Hypsarrhythmia

Infantile Spasms: Treatment

ACTH  Benzodiazepine
Steroids  FBM
Vigabatrin (esp TS)  TPM
B6  ZNS
VPA  KTG diet
VGB  TGB
Surgery

Lennox-Gastaut Syndrome (LGS)

- Multiple seizure types, including:
  - tonic seizures
  - atonic seizures
  - atypical absence seizures
  - myoclonus
- EEG demonstrates generalized slow spike and wave discharges
  - slow background
- Cognitive/motor impairments

LGS: Epidemiology

- LGS is associated with 17% of all profound mental retardation in the general population
- Mortality rate is approximately 10% among children < 11 years of age
LGS: Epidemiology

- Metropolitan Atlanta Development Disabilities Study:
  - prevalence = 2.6/10,000
  - accounts for 4% of all childhood epilepsy
  - approximately 39% have a history of infantile spasms
  - mental retardation was noted in 91%

Trevathan E et al, Epilepsia 1997;38:1283-1288

Types of Seizures in 120 Patients with LGS*

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic</td>
<td>71%</td>
</tr>
<tr>
<td>Atonic</td>
<td>36%</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>21%</td>
</tr>
<tr>
<td>Atypical absence</td>
<td>49%</td>
</tr>
<tr>
<td>Tonic-clonic or clonic</td>
<td>37%</td>
</tr>
<tr>
<td>Partial</td>
<td>24%</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>21%</td>
</tr>
<tr>
<td>Febrile convulsions</td>
<td>10%</td>
</tr>
</tbody>
</table>

*All patients have multiple types of seizures

Modified from Aicardi, 1988

LGS: Diagnostic Criteria

- Two or more seizures types including those that result in falls
  - atonic
  - tonic
  - GTC
  - and/or massive myoclonic seizures
- Onset of epilepsy before age 11
- Abnormal background and slow spike and wave (<2.5 Hz) on EEG

Trevathan E et al, Epilepsia 1997;38:1283-1288.

LGS: Treatment

- Valproate
- Benzodiazepines
  - intermittent
- Newer AEDs
- VNS
- Corpus callosotomy
VNS for LGS

<table>
<thead>
<tr>
<th>N</th>
<th>Mean Age, years (range)</th>
<th>Follow-Up, months</th>
<th>% Change Seizure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horrig, 1997</td>
<td>6</td>
<td>9 (6-13)</td>
<td>21-29</td>
</tr>
<tr>
<td>Hossain, 1999</td>
<td>13</td>
<td>16 (4-44)</td>
<td>6-9</td>
</tr>
<tr>
<td>Lundgren, 1998</td>
<td>4</td>
<td>9.5 (4-19)</td>
<td>11-17</td>
</tr>
<tr>
<td>Parker, 1999</td>
<td>10</td>
<td>10.5 (6-16)</td>
<td>6-12</td>
</tr>
<tr>
<td>Ben-Menachem, 1999</td>
<td>8</td>
<td>?</td>
<td>3-64</td>
</tr>
<tr>
<td>Summary</td>
<td>43</td>
<td>11.6 (4-44)</td>
<td>3-64</td>
</tr>
</tbody>
</table>

Absence Epilepsy

- Age and seizure dependent syndromes
  - CAE
  - JAE
  - JME
Absence Epilepsy

- Treatment
  - ETX
  - VPA
  - LTG
  - ZNS
  - TPM
  - LVT
  - FBM

Febrile Seizures

- A seizure occurring in childhood after age 1 month associated with a febrile illness ($T \geq 38.3^\circ C$)
- Exclusions
  - prior unprovoked seizures
  - acute CNS infection
  - electrolyte imbalance
  - other acute symptomatic events

Febrile Seizures

- No clear upper age limit
  - Max occurrence 18 mo
- Complex features
  - prolonged (>10 or >15 minutes)
  - focal
  - multiple (same illness)

Febrile Seizure

- 2%-5% of children (N. America and Europe)
- Strongly age-dependent
  - 4% before 6 months
  - 90% within first 3 years
  - 6% after age 3
- 30% recurrence rate

Incidence of Febrile Convulsions

![Incidence Curve](image)

JUST SAY NO!

AEDs and Febrile Seizures
Freeman, 1990
Febrile Seizures and MTS
Human Studies
• Retrospective studies
  – Support the notion that seizures early in life, especially complicated FS, may produce MTS
• Prospective studies
  – Do not provide any direct link between one seizure early in life and MTS
• Two-Hit Hypothesis
  – Seizure/seizure
  – Initial precipitating event/seizure

Childhood Partial Seizure Localization
• Extratemporal more common in children
• Prominence of neocortical (posterior or basilar) temporal vs mesial temporal
• “Secondary” generalized epilepsy
• Multifocal

Benign Epilepsy with Centrottemporal Spikes (BECT, Rolandic)
• Age 4-12 years, normal neurologically
• Seizures: 60-80%
  – clonic movements of face or hand
  – tingling face, tongue, hand
  – speech arrest, excessive salivation
  – nocturnal, early AM
• Characteristic EEG
  – sleep activated
  – normal background
• Treatment controversial
• Excellent prognosis

Etiology
• Special syndromes
• Dysplasia
• Neoplasia
  – ganglioglioma
  – DNET
  – hamartoma
• MTS
• Others
• When should surgery be considered?

AED Selection: Age
• Age-related differences in seizure type/syndrome may affect AED selection
• Certain epilepsy syndromes in children may reflect abnormalities during specific brain developmental stages

Diazepam Pharmacokinetics
Mean Plasma Concentrations of Diazepam after IV, rectal solution, IM, tablet, and suppository administration.
AED Selection: Age

- The incidence of epilepsy is higher in patients ages > 75 years
- 50% of all new cases of epilepsy in patients aged > 65 years are complex partial seizures
- Health-related problems may affect AED selection
  - declining intellectual, motor, and sensory functions
  - drug interactions with therapy for comorbidities

Pediatric Epilepsy: Special Considerations

- Clearance rates
  - vary as a function of
    - age group
    - individual maturity
    - comorbidities, specific AED
  - initial and periodic blood level monitoring may help

AED Delivery Systems for Children: Options to Simplify Therapy

- Extended-release
- Suspension
- Syrup
- Sprinkle capsules
- Chewable tablets
- Dispersible tablets
- Sublingual
- IV/IM
- Rectal

AEDs and Seizure Aggravation

- Difficulty estimating drug-induced seizure increase because
  - childhood epilepsies are often subject to seizure frequency fluctuations
  - AEDs can be wrongly ascribed to be the culprit if exacerbation occurs when a new AED is started
  - AED trials are not designed to assess for seizure aggravation
AEDs and Seizure Aggravation

- Paradoxical increase in seizures occurs via 2 separate mechanisms
  - drug intoxication
  - primary drug action

Early Seizure Outcomes in Children

- 595 followed over 2 years:
  - good (remission) 52.8%
  - intermediate 38.3% - 64.7%
  - problems with Rx
    - bad (intractable) 7.7%

  Berg, 2001

Early Seizure Outcomes in Children

- 390 followed over 4 years:
  - early good and bad outcomes persisted in 80%
  - ~ 50% intermediate 2 years later achieved remission
    - 8% intractable
    - 37% remained intermediate

  Berg, 2001