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%
- Tonic-clonic 19%
- Simple partial 11%
- Complex partial 11%
- Myoclonic 7%
- Other generalized 11%
- Unknown/multiple 5%
- 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

- Early myoclonic epilepsy (Aicardi’s syndrome)
- Early infantile epileptogenic encephalopathy (Ohtahara syndrome) (myoclonus, tonic/burst suppression)
- Benign familial neonatal convulsions
- Benign neonatal convulsions (clonic/normal or sharp theta)
- Neonatal Abnormal Exam Normal Exam Age Group
- West’s syndrome (spasms/hypsarrhythmia)
- Severe infantile myoclonic (Dravet syndrome) (myoclonus, FS, partial/GSW, PPR); Migrating seizures (hypomotor, other/multifocal spikes)
- Benign infantile spasms (Lombroso)
- Benign myoclonic epilepsy (myoclonus/GSW); Benign infantile seizures (various descriptions, normal)

Diagnostic Approach: Seizure Semiology/EEG Finding

- Benign infantile spasms (Lombroso), Benign myoclonic epilepsy (myoclonus/GSW), Benign infantile seizures (various descriptions, normal)
- Epilepsia partialis continua syndromes (Kojewnikoff, Rasmussen) (epilepsia partialis continua/polymorphic spikes)

Diagnostic Approach: Seizure Semiology/EEG Finding

- 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)
- Progressive myoclonus (myoclonus, other/slowed background)

Diagnostic Approach: Seizure Semiology/EEG Finding

- Lennox-Gastaut (tonic seizures, atypical absence, partial/slow, ie, 2.5-Hz spike-wave)

Diagnostic Approach: Seizure Semiology/EEG Finding

- West’s syndrome (spasms/hypsarrhythmia); Severe infantile myoclonic (Dravet syndrome) (Myoclonus, FS, partial/GSW, PPR); Migrating seizures (hypomotor, other/multifocal spikes)

Diagnostic Approach: Seizure Semiology/EEG Finding

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Epidemiology: Seizure Type and Epilepsy Syndrome

- In children, the majority (¼ to ⅔) of seizures and epilepsy syndromes are partial-onset
- This compares with 75% to 90% in adults

Researchers Patient Sample n % Partial
- Sillanpaa et al (Turku, Finland) Population-based 235 64
- Berg et al (Conn, US) Community-based 613 59

GSW = generalized spike waves; FS = febrile seizures; PPR = photoparoxysmal response

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

**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 Ictal Event

LGS: Treatment

- Valproate
- Benzodiazepines
  - intermittent
- Newer AEDs
- VNS
- Corpus callosotomy
### LGS Treatment: Drop Attacks

![Graph showing % of seizure reduction for different treatments.]

- **Felbamate (FBM)**: Placebo 1 (n=37), placebo 2 (n=75), placebo 3 (n=46)
- **Lamotrigine (LTG)**: Placebo 2 (n=89), placebo 3 (n=49)
- **Topiramate (TPM)**: Placebo 3 (n=49)

**Results:**
- *P* = .01
- *P* = .04

References:

### LGS Treatment: GTC Seizures

![Graph showing % of seizure reduction for different treatments.]

- **Felbamate (FBM)**: Placebo 1 (n=13), placebo 2 (n=64), placebo 3 (n=21)
- **Lamotrigine (LTG)**: Placebo 2 (n=60), placebo 3 (n=64)
- **Topiramate (TPM)**: Placebo 3 (n=17)

**Results:**
- *P* = .017
- *P* = .03
- *P* = < .01

References:

### VNS for LGS

<table>
<thead>
<tr>
<th>Study</th>
<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>
<td>58%, &gt; 90% reduction</td>
</tr>
<tr>
<td>Hossain, 1999</td>
<td>13</td>
<td>16 (4-44)</td>
<td>6-9</td>
<td>-52% (0%-23%)</td>
</tr>
<tr>
<td>Lundgren, 1998</td>
<td>4</td>
<td>9.5 (4-19)</td>
<td>11-17</td>
<td>-31% (0%-57%)</td>
</tr>
<tr>
<td>Parker, 1999</td>
<td>10</td>
<td>10.5 (6-16)</td>
<td>6-12</td>
<td>-24% (+40%-100%)</td>
</tr>
<tr>
<td>Ben-Menachem, 1999</td>
<td>8</td>
<td>?</td>
<td>3-64</td>
<td>-50% (0%-100%)</td>
</tr>
<tr>
<td>Summary</td>
<td>43</td>
<td>11.6 (4-44)</td>
<td>3-64</td>
<td>34-90%</td>
</tr>
</tbody>
</table>

Reference:

### Comparison of Childhood Absence, Juvenile Absence and Juvenile Myoclonic Epilepsy

<table>
<thead>
<tr>
<th></th>
<th>Childhood</th>
<th>Juvenile</th>
<th>JME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>3-12 years</td>
<td>Puberty</td>
<td>Puberty</td>
</tr>
<tr>
<td>Frequency</td>
<td>Multiple daily</td>
<td>Rarely daily</td>
<td>Variable</td>
</tr>
<tr>
<td>EEG eleptiform activity</td>
<td>3 Hz spike-wave</td>
<td>3.5-4 Hz spike-wave</td>
<td>3.5-6 Hz spike-wave</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Favorable</td>
<td>Favorable</td>
<td>Favorable</td>
</tr>
<tr>
<td>Length of therapy</td>
<td>1-2 years</td>
<td>+/-</td>
<td>Lifelong</td>
</tr>
</tbody>
</table>

### Absence Epilepsy

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

References:
- Parker, 1999
- Ben-Menachem, 1999
- Lundgren, 1998
- Horrig, 1997
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°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

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 Centrotemporal 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

Diazepam Pharmacokinetics

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
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

Pediatric Epilepsy: Special Considerations

- Adverse effects
  - idiosyncratic
    - hematologic
    - dermatologic
    - hepatic
  - behavioral
    - aggression
    - mania
    - concentration
    - memory difficulties

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