Neuropsychological Outcomes of Pediatric Epilepsy

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Objectives

• Cognitive
• Behavioral
• Risk factors
1. Definitions, epidemiology, diagnosis, & seizure classification
2. Neuropsychological outcomes (all epilepsy)
3. Absence epilepsy
4. Treatments of epilepsy and impact on neurocognitive outcomes
Definitions, Epidemiology, Diagnosis, & Classifications
Definitions

- **Seizures**: abnormal synchronous firing of neural networks with change in functioning
  - Abnormal neuronal firing temporarily interferes with muscle control, movement, speech, vision, and/or consciousness

- **Epilepsy**: not a specific disease, but a condition describing chronic, recurring seizures

- Generally, seizure disorders are only diagnosed when an individual has more than one “unprovoked” seizures
Definitions

• Seizure semiology: the behavioral manifestations (description) of a seizure
• Aura: sensation or physiological warning of impending seizure
  – Strange feeling
  – Often sensory
• Ictal (intraictal): occurring during a seizure
  – Postictal period: Just what you think it means
  • Can be associated with fatigue, confusion, depression
  – Interictal period: time between seizures
Epidemiology of Pediatric Epilepsy

• ~5-10% of children will experience at least one seizure
• ~0.5%-1% of children develop epilepsy before age 20
• Most common age for seizure onset is 1-4 yrs
• Slightly higher occurrence in boys than girls
• Specific etiology identified in only approximately 30% of cases (this may change with improved imaging)
Seizure Diagnosis

• Clinical presentation and history
• EEG
  – A single recording often normal in 30-40% of pediatric cases
  – Provocation methods include hyperventilation (absence), photic stimulation, and sleep deprivation
  – PEMU hospitalization with video EEG is often seen as “gold standard”
• Differentials: psychogenic non-epileptic seizures, breath holding (infants), reflux, migraines, hypoglycemia, cardiovascular events (syncope), transient ischemic attacks, daydreaming
Classification of Seizures

• **Partial (focal) seizures**
  – Initiated by neuronal firing in circumscribed brain area (i.e., the “focus”)
  – Secondarily generalized seizures: spread throughout the brain
  – Further classified according to impact on consciousness
    • **Simple Partial**: No alteration in consciousness
    • **Complex Partial**: Alteration in consciousness
Classification of Seizures

- **Generalized Seizures** - Initiated by neuronal firing in both hemispheres
  - Generalized tonic-clonic (grand mal)
  - Typical absence seizures (petite mal)
    - Sudden onset of impaired consciousness (typically <30”)
    - Characteristic 3/s spike-wave discharges on EEG
    - Can be associated with automatisms
  - Atypical Absence
    - EEG more heterogeneous than typical absence
    - Longer in duration than typical absence
  - Myoclonic seizures:
    - brief, shock-like jerks of a muscle or group of muscles
  - Atonic seizures: sudden loss of tone “drop attacks”
  - Tonic seizures: sudden stiffening in body, arms, or legs
    - Most often occur during sleep
Classification of Seizures

Partial
- Simple
- Complex
  - Secondary Generalization

Generalized
- Absence
- Convulsive
- Tonic
- Clonic
- Tonic- Clonic
- Clonic-Tonic- Clonic

Secondary Generalization
- Clonic
Epilepsy Classification

• Yea, but it can’t be that simple . . .
• Epilepsies can be classified in any of 5 different ways:
  – Seizure localization (just reviewed)
  – Etiology
  – Semiology features
  – As part of identifiable medical syndromes (e.g. gelastic seizures with HH)
  – By the events that trigger seizures (e.g. photosensitive epilepsy)
Etiology

– **Symptomatic:** identified cause
  - Medical condition/injury (e.g., TBI, CNS infection, neoplasm)
  - Malformation (e.g. Sturge Weber, Dandy Walker Syndrome, lissencephaly)
  - Cortical dysplasia

– **Cryptogenic:** no identified cause identified, but implies an underlying cause exists, but can’t be identified

– **Idiopathic:** unknown cause and without underlying neurological abnormality
Cortical Dysplasia and Epilepsy

• Cortical dysplasia (CD) is abnormal growth of brain cells that is often observed as focal cortical thickening on MRI (though not always visible)

• The neurons that develop in these regions are abnormally developed and/or often much larger than normal
  – The balloon cell neuron is one such large neuron that is characterized by enlarged cytoplasm, displaced nucleus, and lack of dendrites
Cortical Dysplasia
Mesial Temporal Lobe Sclerosis

- Typically associated with temporal lobe epilepsy
- Vulnerability of hippocampus to injury:
  - TBI, anoxia
  - Seizures
    - Febrile seizures
    - Status epilepticus
- Implications for temporal lobectomy
- Associated memory impairments (adults?)
  - Baxendale et al., 1998;
    Hermann et al., 2002
The Role of the Pediatric Neuropsychologist

• Neurocognitive assessment:
  – Monitor changes over time due to epilepsy / treatment
    • Medication changes
    • Pre-post neurosurgical intervention
  – Localization / lateralization
    • Neuropsych profile
    • Wada and fMRI testing
  – School and treatment programming

• Diagnostic clarification
  – e.g. staring spells, psychogenic nonepileptic seizures

• Secondary diagnoses (e.g. depression, AD/HD)

• Behavioral health recommendations
Neurocognitive Outcomes
All Epilepsy Types

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ARE YOU LEFT-BRAINED OR RIGHT-BRAINED?

PERSONNEL

I TRY TO AVOID POLITICS ENTIRELY!

search ID: hsc1503
Epilepsy is not a single condition!
Cognitive Risk Factors

• Neurological
  – EEG abnormalities (slow wave activity)
  – Positive neuroimaging
  – Epileptic syndromes (e.g. CSWS)

• Seizure
  – Onset before age 5
  – Frequency
  – Duration
  – Poor seizure control / refractory
  – Cluster seizures
  – Multiple seizure types
  – Status epilepticus

• Medications
  – Polytherapy
Cognitive Risk Factors (cont.)

• **Status Epilepticus (SE)**
  - Generalized convulsive status epilepticus (GCSE): a seizure that lasts 30 minutes (though some say as brief as 5 minutes) or two or more seizures between which individuals do not recover
  - Nonconvulsive status epilepticus (NCSE): difficult to define and monitor (outside of PEMU).
  - SE associated with significant mortality and morbidity
Cognitive Risk Factors (cont.)

• Localization in NP profile
  – Long history of lateralization in adults (e.g. memory in TLE), but the research less robust in children. Potential explanations:
  • Plasticity of the developing brain
  • Changes in neurocognitive constructs over the course of development
  • Loss of skills V.S. failure to develop
  – Memory findings follow lateralizing patterns (i.e. Jambaque et al., 1993)
    • Left TLE: Deficits on list learning and narrative recall
    • Right TLE: Deficits on figure recall and abstract visual designs
    • Bilateral TLE: Deficits on both
  – Piccirilli (1988)
    • Visual spatial processing effected in children with right side or bilateral, but not left side focus
    • Children with left side focus showed atypical language
    • Children with frontal lobe foci
      – Perform worse on measures of response inhibition and planning than TLE
      – Fine motor slowing appears more prevalent
Cognitive Risk Factors (cont.)

• Child and family factors
  – Low SES
  – Poor adaptive resources
Intellectual Outcomes

Epilepsy
- >80: 5%
- 70-80: 3%
- 60-69: 7%
- <60: 11%
- Impaired NOS: 11%

74%

IGE
- >80: 5%
- 70-80: 3%
- 60-69: 6%
- <60: 6%
- Impaired NOS: 6%

86%

Normative
- >80: 8%
- 70-80: 1%
- 60-69: 1%
- <60: 90%

Adapted from Berg et al. (2008); n = 566
Neuropsych Impact

• Language
  – Expressive skills often more impaired than receptive
  – Reorganization of language can occur if seizures involve the left hemisphere and occur early

• Visual-Spatial
  – Perceptual and visual-motor integration difficulties in some disorders
Neuropsych Impact

• Memory
  – Memory impairments noted in many epilepsy groups relative to controls
  – IGE typically better than temporal lobe epilepsies, particularly on list learning tasks (Jambaque et al., 1993)

• Attention
  – Most consistent area of deficit across seizure types
  – Deficits of sustained attention, persist even when AED status is accounted for

• Executive Functions
  – Reasoning and cognitive flexibility deficits observed in many epilepsy groups

• Fine Motor
  – Reaction time and psychomotor slowing common
Academic Outcomes

• Heightened risk of negative academics compared to other medical conditions (e.g. arthritis, asthma)
  – Poorer academic achievement
  – Poorer academic performance
  – Risk of retention
  – Higher frequency of LD
Behavioral Impact

- Increased psychiatric disturbance
  - (McDermott et al., 1995)
    - 8% general population
    - 20% of children with cardiac disease
    - 31% of children with epilepsy
    - ADHD 6X more common than population, often inattentive

- Behavioral and emotional disruption linked to cognitive deficits
  - Children with idiopathic epilepsy and normal cognitive abilities do not appear at greater risk than non-neurological population

- Family factors likely moderate the impact of some behavioral difficulties (e.g. defiance, aggression)
  - (Pianta & Lothman, 1994)
Epilepsy and Autism

• Challenging as both are heterogeneous disorders

• Estimates of comorbidity vary dramatically:
  – Early estimates suggested a comorbidity of 20-30%
  – Berg, Plioplys, & Tuchman (2011)
    • (n=560) 5% of children with epilepsy had autism
      – higher than population (.5%-1%)
    • West syndrome, cognitive impairment, and male gender were risk factors
  – Likely dependent on epilepsy type
    • E.g. 40% of patients with tuberous sclerosis complex
      Numis et al. (2011)
Absence Epilepsy

"The prefrontal cortex is involved in higher mental functioning, like using a can opener and remembering to feed you."
General Information

• Absence epilepsy ~8% of all epileptic conditions in school-aged children
• Often associated with GTC seizures
• Divided into:
  – childhood absence epilepsy (CAE)
  – adolescent absence epilepsy (AAE)
CAE Neuropsych Outcomes

- Pavone et al. 2001

<table>
<thead>
<tr>
<th>Function</th>
<th>Early onset absence epilepsy (&lt;4 y)</th>
<th>Absence epilepsy (&gt;4 y)</th>
<th>Total patients with absence epilepsy</th>
<th>Control group</th>
<th>Statistical analysis, p</th>
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<tr>
<td>General cognition</td>
<td>5</td>
<td>37</td>
<td>25</td>
<td>55</td>
<td>&lt;0.05</td>
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<tr>
<td>Language</td>
<td></td>
<td>43</td>
<td>54</td>
<td>80</td>
<td>NS</td>
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<td>Visual-spatial skills</td>
<td>16</td>
<td>39</td>
<td>31.9</td>
<td>62</td>
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<td>Verbal memory</td>
<td></td>
<td>76</td>
<td>80</td>
<td>69</td>
<td>NS</td>
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<tr>
<td>Nonverbal memory index</td>
<td>13</td>
<td>62</td>
<td>49.9</td>
<td>71</td>
<td>&lt;0.05</td>
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<tr>
<td>Composite memory index</td>
<td></td>
<td>65</td>
<td>69</td>
<td>65</td>
<td>NS</td>
</tr>
<tr>
<td>Delayed recall index</td>
<td>13</td>
<td>27</td>
<td>23.7</td>
<td>65</td>
<td>&lt;0.01</td>
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</table>

Values are percentiles. p < 0.05 is significant.
• Caplan et al. (2008)
  – CAE (n=69) v.s. controls (n=103)
  – Lower intellectual scores, including both Verbal IQ and Performance IQ
  – Poorer performance on Test of Language Development.

  • Potential interpretations:
    – CAE more vulnerable to language impact than mixed absence group?
    – Differing measures than Pavone
    – Ethnicity was a significant predictor of language in this study
    – Language differences between populations
Nolan et al. (2004) compared children with CAE, TLE, and FLE on IQ and memory tasks

- IQ did not significantly differ, although slightly higher in CAE (M=94) than FLE (M=85) and TLE (M=90)
- CAE
  - Better performance than FLE and TLE on most verbal and nonverbal memory tasks
  - Although slightly lower than published norms, performance did not significantly differ from controls, except with:
    - Rey Complex Figure Recall
    - Finger Windows (Nonverbal Working Memory)
CAE Neuropsych Outcomes

- Attention
CAE Neuropsych Outcomes

- Fine Motor
  - Bhise et al. (2009) cont.

Grooved Pegboard

<table>
<thead>
<tr>
<th>T-Score</th>
<th>Dominant</th>
<th>Nondominant</th>
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<tr>
<td>80</td>
<td></td>
<td></td>
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<td>70</td>
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<tr>
<td>60</td>
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<tr>
<td>50</td>
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<tr>
<td>40</td>
<td></td>
<td></td>
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<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
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- Generalized
- Absence
- Convulsive
- Focal
CAE Emotional/Behavioral

- Caplan et al. (2008)

<table>
<thead>
<tr>
<th>Psychiatric diagnosis</th>
<th>CAE</th>
<th>Normal</th>
<th>X²</th>
<th>df</th>
<th>p</th>
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<tr>
<td>Yes</td>
<td>61%</td>
<td>15%</td>
<td>23.07</td>
<td>1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>39%</td>
<td>85%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Type of diagnosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ADHD</td>
<td>26%</td>
<td>6%</td>
<td>13.59</td>
<td>1</td>
<td>0.0002</td>
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<tr>
<td>Affective/anxiety</td>
<td>20%</td>
<td>7%</td>
<td>6.42</td>
<td>1</td>
<td>0.01</td>
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<tr>
<td>ADHD + Affective/anxiety</td>
<td>11%</td>
<td>2%</td>
<td>5.99</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>0%</td>
<td>2.22</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>CBCL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>40.0%</td>
<td>11.8%</td>
<td>15.49</td>
<td>1</td>
<td>0.001</td>
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<tr>
<td>Internalizing</td>
<td>36.9%</td>
<td>15.7%</td>
<td>9.6</td>
<td>1</td>
<td>0.002</td>
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<tr>
<td>Externalizing</td>
<td>26.2%</td>
<td>6.9%</td>
<td>6.9</td>
<td>1</td>
<td>0.008</td>
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<tr>
<td>Attention</td>
<td>37.5%</td>
<td>4.9%</td>
<td>15.50</td>
<td>1</td>
<td>0.001</td>
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<tr>
<td>Somatic complaints</td>
<td>34.4%</td>
<td>5.9%</td>
<td>20.42</td>
<td>1</td>
<td>&lt;0.0001</td>
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<tr>
<td>Social problems</td>
<td>23.4%</td>
<td>5.9%</td>
<td>6.07</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>Thinking</td>
<td>20.3%</td>
<td>3.9%</td>
<td>7.67</td>
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<td>0.005</td>
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<td>Withdrawn</td>
<td>14.1%</td>
<td>2.9%</td>
<td>4.17</td>
<td>1</td>
<td>0.04</td>
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<td>Anxious/depressed</td>
<td>17.2%</td>
<td>7.8%</td>
<td>2.34</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Aggressive</td>
<td>9.4%</td>
<td>2.0%</td>
<td>1.68</td>
<td>1</td>
<td>NS</td>
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<tr>
<td>Delinquent</td>
<td>14.1%</td>
<td>6.9%</td>
<td>0.70</td>
<td>1</td>
<td>NS</td>
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</table>

ADHD, attention deficit disorder; NS, not significant.
### AE Psychosocial Outcomes

- **Wirrell et al. (1997)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AE %</th>
<th>JRA %</th>
<th>Odds</th>
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<tbody>
<tr>
<td>Drop out high school</td>
<td>36</td>
<td>14</td>
<td>3.7</td>
</tr>
<tr>
<td>Repeat grade</td>
<td>48</td>
<td>23</td>
<td>3.1</td>
</tr>
<tr>
<td>Not attend college/university</td>
<td>71</td>
<td>39</td>
<td>3.8</td>
</tr>
<tr>
<td>Behavioral problems at school</td>
<td>41</td>
<td>10</td>
<td>6.4</td>
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<tr>
<td>Psychiatric Diagnoses</td>
<td>54</td>
<td>31</td>
<td>2.6</td>
</tr>
<tr>
<td>Unplanned pregnancy</td>
<td>34</td>
<td>3</td>
<td>19.3</td>
</tr>
<tr>
<td>Heavy drinking</td>
<td>39</td>
<td>16</td>
<td>3.3</td>
</tr>
<tr>
<td>Poor sibling relationships</td>
<td>19</td>
<td>5</td>
<td>4.1</td>
</tr>
<tr>
<td>Months full time work last year</td>
<td>7.6</td>
<td>9.3</td>
<td>P&lt;.02</td>
</tr>
<tr>
<td>Unskilled laborer</td>
<td>53</td>
<td>16</td>
<td>5.9</td>
</tr>
</tbody>
</table>
Ketogenic Diet

• Developed in the 1920s, when AEDs not widely available
• A high-fat, low-carbohydrate diet used to control seizures
  – Fast until ketosis, then 80% of calories from fat
• Following diet for 1 year proved effective in reducing reported incidence (i.e., at least 50% reduction) of seizure activity in some cases of intractable, generalized seizure disorder (Freeman et al., 1998)
Vagus Nerve Stimulator (VNS)

- Pacemaker-sized device implanted in upper left part of chest with wire leads connecting to vagus nerve in left side of neck
  - Implanted to stimulate the vagus nerve in individuals with intractable complex partial or generalized seizure disorder
- After 12 months of VNS, 45% of people had fewer seizures—with 20% of those people reducing their seizure frequency by 75% (Schachter, 2002)
Neurosurgery

Temporal lobectomy
– Most common and successful type of epilepsy surgery
– Up to 80% seizure-free with surgery

• Corpus callosotomy
  – Most effective for atonic, tonic-clonic, and tonic
  – Seizure frequency reduction of 70-80%
  – May have nondominant neglect or disconnection syndrome

• Hemispherectomy
  – More than 75% experience complete or virtually complete seizure control in lateralized epilepsy (e.g., Sturge-Weber, Rasmussen)
  – “Functional hemispherectomy” minimizes amount of tissue removed
Antiepileptic Drugs (AEDs)

• About 75% of patients of all ages reach remission on AEDs
• Effects on cognition are generally modest
  – Largest attention and psychomotor speed
• General risk factors include:
  – Polytherapy
  – Higher dosages
  – Rapid titration
Antiepileptic Drugs (AEDs)

- Newer AED’s generally fewer effects than older
- Phenobarbital:
  - High rate of discontinuance d/t hyperactivity
  - Children with phenobarbital prophylaxis for febrile seizures in infancy/preschool
    - Lower IQ
    - Poorer academic outcomes for up to 3-5 years (Sulzbacher et al., 1999)
- Topiramate: somnolence, slowing, memory problems, and language difficulties
  - Effects generally seen in a small subset of patients
    - Individual factors have not been identified
Antiepileptic Drugs (AEDs)

- Emotional/Behavioral Effects
  - Gabapentin
    - In children:
      - Emotional lability
      - Hostility and aggression
      - Hyperactivity
  - Age dependent risk, with few adult behavioral side effects

- Keppra
  - Risk of irritability
  - Highest rates of adult psychiatric side effects (Weintraub et al. 2007)
  - Few studies with pediatrics
  - Hostility in 11% of children (Glauser et al. 2004)
  - Other difficulties include:
    - Depression
    - Nervousness
    - Personality change
Conclusions

- Pediatric epilepsy is a heterogeneous group of conditions with variable outcomes
- Neurocognitive and behavioral outcomes are related to epilepsy, as well as other factors
- Treatments (including AED’s) complicate this risk