Determinants of QOL and Psychiatric Comorbidity in Epilepsy In Children

Mary Lou Smith, PhD

Every child deserves a healthy start, a strong mind, and a bright future.
Faculty/Presenter Disclosure
Mary Lou Smith

- Relationships with commercial interests: none
- Speakers Bureau/Honoraria: none
- Consulting Fees: none
- Other: none
- Disclosure of Commercial Support: n/a
- Mitigating Potential Bias: n/a
Overview / Objectives

- Review identified risk factors for poor QOL in children with epilepsy

- For *young children*, review outcomes of treatment for epilepsy on QOL, behaviour and cognitive development
HRQL: A BROAD, MULTI-DIMENSIONAL CONSTRUCT
Risk Factors Associated with HRQL

**Clinical**
- Duration of epilepsy
- Seizure frequency
- Seizure type
- Seizure severity
- AEDs
- Presence of a comorbidity

**Psychosocial**
- Parental anxiety
- Socioeconomic status
- Behaviour problems*
- Cognitive problems*

*Ferro, 2014
Two Canadian Multi-Centre Studies
Canadian Pediatric Epilepsy Network (CPEN)

Health Related Quality of Life in Children with Epilepsy Study
- HERQULES
- Kathy Speechley

Pediatric Epilepsy Surgery and Quality of Life
- PEPSQOL
- Elysa Widjaja and Mary Lou Smith
HERQULES
N= 374, new onset, age 4-18

- Epilepsy Variables
- Family Environment
  - Satisfaction with family relations
  - Resources to aid family adaptation to stressful events
  - Family stress in past year
  - Parental depression
- Comorbidities
  - Behaviour
  - Cognition
HERQULES – Two Year Outcomes

Speechley 2012
HERQULES:
Predictors of Improved QOL over Time

- Absence of cognitive problems
- Fewer AEDs
- Higher family functioning
- Fewer family demands

- Predicted QOL closely tied to cognitive status at baseline
- Cognitive problems may be the “driving force” behind declining QOL over 2 years
PEPSQOL Model of Impact of Surgical and Medical Treatment on HRQL

**GOAL OF MANAGEMENT OF EPILEPSY**

- **Treatment:** Surgical vs Medical
  - Baseline Predictors: Baseline HRQL, Baseline patient factors, Baseline family factors
  - Moderating Factors: Patient Factors, Family Factors
    - Patient Factors: Mood (anxiety & depression), Self-Concept
    - Family Factors: Caregivers’ Mood (anxiety & depression), Family Adaptation, Family Resources, Family Demands
  - Mediating Factor: Clinical Factor: Seizure Control
  - HRQL: Time 0, Time 1, Time 2, Time 3, Time 4

Legend:
- Time 0 = Baseline
- Time 1 = 6 months follow-up
- Time 2 = 12 months follow-up
- Time 3 = 18 months follow-up
- Time 4 = 24 months follow-up
PEPSQOL Baseline Predictors of QOL
N= 115, Medically Refractory, Age 4-18

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<thead>
<tr>
<th>Univariable Models</th>
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Conway 2016
### PEPSQOL Baseline Predictors of QOL

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Conway 2016
Important Take-Home Message

- There are modifiable family and child factors predictive of QOL
- If we recognize and treat those factors, we can improve QOL
Prevalence of Cognitive Comorbidities

- Intelligence
  - Intellectual disability - 25-40 %
  - Mild or subtle intellectual deficits - 30%

- Learning disabilities / Academic problems
  - 70 % - low achievement
  - 40 % - underachievement
ADHD

- Most common psychiatric disorder in pre-school and school-aged children with epilepsy
- Clinic samples: 14-38%
- Predominantly inattentive subtype

Predictors:
- Underlying brain dysfunction
- Frequent seizures / epileptiform discharges
- AED side effects
- Other psychiatric disorders

Not predictive:
- Sex
- Seizure type
- Seizure localization

Treatment: medication

Besag et al., Epileptic Disord, 2016, 18 (Suppl 1), S8-S15
Psychiatric Comorbidities: Depression and Anxiety

Prevalence

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Anxiety</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>5 – 17 %</td>
<td>7 – 13 %</td>
</tr>
<tr>
<td>Clinic</td>
<td>16 – 48 %</td>
<td>10 – 37 %</td>
</tr>
</tbody>
</table>

Most of these cases had NOT been diagnosed prior to study

Risk Factors

- **Predictive:**
  - Lower IQ
  - Language/cognitive deficits
  - Drug-resistant seizures
  - Family variables

- **NOT Predictive:**
  - Age of onset, seizure type, syndrome

Treatment: Medication, CBT, Community Support Groups, Camps

Dunn et al., 2016, Epileptic Disord., 18 (Suppl 1), S24-S30
Risk Factors for Autism in Epilepsy

- Symptomatic epilepsy
- Seizure onset ≤ 1 year
- Early encephalopathic epilepsy
  - West syndrome
  - Dravet syndrome
  - Tuberous sclerosis

Nabbout et al., 2017
How do treatments for epilepsy in young children impact on these comorbidities?

- **Developmental / Cognitive Outcomes**
  - Surgery
  - Ketogenic diet
  - Medical treatment of infantile spasms

- **Psychiatric / behavioural outcomes**
  - Surgery
<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>Range (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age at Preoperative assessment</strong></td>
<td>12</td>
<td>3.3 – 33.1</td>
</tr>
<tr>
<td><strong>Age at Surgery</strong></td>
<td>14</td>
<td>3 - 34</td>
</tr>
<tr>
<td><strong>Age at Postoperative assessment</strong></td>
<td>24</td>
<td>10 - 53</td>
</tr>
</tbody>
</table>

Loddenkemper et al., 2007
## Cleveland Clinic
### Surgery < 3 years of age

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median DQ</td>
<td>37</td>
<td>49</td>
</tr>
<tr>
<td>DQ &lt; 70</td>
<td>91 %</td>
<td>75 %</td>
</tr>
</tbody>
</table>

Mean DQ in typically developing children = 100

Decline in DQ more likely in children with preoperative DQ > 50 (75% vs. 6%)

Loddenkemper et al., 2007
Seizure and Surgical Variables

- Not associated with postoperative development
  - Pre- and post-operative seizure frequency
  - Post-operative seizure freedom
  - Change in AEDs
  - Side of surgery
  - Type of resection
  - Pathology

Loddenkemper et al., 2007 – Cleveland Clinic
Timing of Surgery

Younger age at time of surgery correlated with improvement in DQ

Loddenkemper et al., 2007 – Cleveland Clinic
### UCLA: Surgery for Symptomatic Infant-onset Epileptic Encephalopathy

<table>
<thead>
<tr>
<th></th>
<th>Active IS</th>
<th>Treated IS</th>
<th>No history of IS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 55</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at seizure onset (years)</td>
<td>0.2 ± 0.2</td>
<td>0.2 ± 0.3</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>Age at surgery (years)</td>
<td>1.2 ± 1</td>
<td>3.3 ± 3.4</td>
<td>5.0 ± 4.3</td>
</tr>
<tr>
<td>Onset to surgery (years)</td>
<td>1.1 ± 0.9</td>
<td>3.0 ± 3.4</td>
<td>4.6 ± 4.1</td>
</tr>
</tbody>
</table>

Jonas et al., 2005
Early Surgery: Epileptic Encephalopathy

Outcome: Adaptive Behaviour
Mean Follow-Up: 1.8 years

- Active IS
- Successful Treatment
- No Hx IS
- Typical Development

Jones et al., 2005 - UCLA
Effect of Seizures

Jonas et al., 2005 - UCLA
### Surgery ≤ 7 years: Bethel

<table>
<thead>
<tr>
<th></th>
<th>N = 50</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td>Age at seizure onset</td>
<td>14 months (1.14)</td>
<td>1 – 52 months</td>
<td></td>
</tr>
<tr>
<td>Age at surgery</td>
<td>4.99 years (1.0)</td>
<td>3 – 7 years</td>
<td></td>
</tr>
<tr>
<td>Duration of epilepsy</td>
<td>3.77 years (1.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>before surgery</td>
<td></td>
<td></td>
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Freitag & Tuxhorn, 2005 - Bethel
FIG. 1. Preoperative cognitive function compared to normal distribution.

Freitag & Tuxhorn, 2005 - Bethel
## Cognitive Outcomes

<table>
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<th>Length of Follow-Up</th>
<th>6 – 12 mos (n = 50)</th>
<th>2 - 3 years (n = 40)</th>
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<tbody>
<tr>
<td>Unchanged</td>
<td>82 %</td>
<td>72 %</td>
</tr>
<tr>
<td>Gain</td>
<td>9 %</td>
<td>22.5 %</td>
</tr>
<tr>
<td>Loss</td>
<td>9 %</td>
<td>4.5 %</td>
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Freitag & Tuxhorn, 2005 - Bethel
Cognitive gains seen almost exclusively in seizure-free children, but so were cognitive losses.

Freitag & Tuxhorn, 2005 - Bethel
Ketogenic Diet

- Largely anecdotal evidence and parent report
- Improved alertness, cognitive function, behaviour
- Improvement in sleep may contribute to improvement in alertness

Hallbrook, 2011; Ijff et al., 2016)
### Treatment for IS: 4 yr outcomes

<table>
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<tr>
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<th>Hormone Therapy</th>
<th>Vigabatrin</th>
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<td>All cases N = 77</td>
<td>Median: 60 Quartile (42,97)</td>
<td>Median: 50 Quartile (36, 67)</td>
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Epilepsy outcome not affected by type of treatment

Earlier initiation of treatment → better developmental outcomes

UKISS: Darke et al., 2010
## Treatment for IS: 4 yr outcomes

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<tr>
<td>No Identified Etiology N = 37</td>
<td>Median: 96</td>
<td>Median: 63</td>
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<tr>
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<td>Quartile (52,102)</td>
<td>Quartile (37, 92)</td>
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UKISS: Darke et al., 2010
Outcome of ASD in Epilepsy

- Independent of epilepsy outcome
- Depends on early, intensive intervention
- Cognitive impairment worse in ASD + epilepsy than ASD alone

(Danielsson et al., 2005; Nabbout et al., 2017)
IS: Developmental Outcome by Autism Status

Bitton et al., Epilepsia, 56(6):856–863, 2015
Epilepsy Surgery: Psychiatric Outcomes

- Assessed before & 2 years after surgery

Prior to surgery:
- 14/24 had psychiatric diagnosis (7 > 1)
- Most common: PDD and ADHD
- Only 4 had been diagnosed prior to surgical workup

Follow-up
- 16/24 had psychiatric diagnosis (11 > 1)
- New cases of anxiety and depressive disorders

Danielsson et al., 2002
Epilepsy Surgery: ASD Outcomes

- 5 children with ASD
  - 2 mild ID, 3 severe ID
  - 3 hyperactive

- 2 years after surgery:
  - Diagnoses persisted
  - Some improvement in severity of symptoms in 3

Danielsson et al., 2009
### Temporal lobectomy in childhood: Great Ormond Street Series

#### Percent with diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Pre</th>
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<td>Pervasive Developmental Disorder</td>
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# Temporal lobectomy in childhood: Great Ormond Street Series

Percent with diagnosis

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Conclusions

- Treatment of epilepsy itself may not always result in large changes in children’s developmental, cognitive, psychiatric and QOL outcomes
- Early treatment is important
- Does treatment from epilepsy prevent worsening?
- Many psychiatric comorbidities go unrecognized – please screen your patients!
- Need to direct treatment at the comorbidities themselves
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CIHR IRSC

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