THE NEUROLOGY OF RETT SYNDROME: SEIZURES AND SLEEP

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WHY SEIZURES AND SLEEP?

• Both are Frequent Problems
• Both Impact on Health and Quality of Life
• Seizures and Sleep are Interrelated
• Both are Treatable
SEIZURE BASICS

• Epilepsy = Recurrent Seizures

• Seizure = Excessive, Repeated Firing of Neurons ("Brain cells")

• Seizure = Symptom of Brain Problem
Rett Syndrome: Seizures

WHAT WE HAVE LEARNED FROM THE NATURAL HISTORY STUDY
Seizures and Rett Syndrome

- MECP2 mut: 57.5%
- No MECP2 mut: 71.7%
- Total group: 60%
- Typical: 60%
- Atypical: 61%

Number of participants
MECP2 and Seizure

Number of participants

- C terminal deletion: 69%
- Lg deletion: 57%
- R306C: 49%
- R294X: 69%
- R270X: 53%
- R255X: 49%
- R168X: 54%
- T158M: 74%
- R133C: 50%
- R106W: 78%
## Presence of Epilepsy and Severity

<table>
<thead>
<tr>
<th>CSS Subscale Score Category</th>
<th>N=346 (Epilepsy-YES)</th>
<th>N=208 (Epilepsy-NO)</th>
<th>p Value Adjusted for Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CSS (Mean)</td>
<td>25.2 ± 7.7</td>
<td>20.2 ± 6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ambulation (Mean)</td>
<td>2.8 ± 2.0</td>
<td>2.3 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hand Use (Mean)</td>
<td>2.0 ± 1.0</td>
<td>1.6 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Language (Mean)</td>
<td>3.1 ± 0.7</td>
<td>2.9 ± 0.6</td>
<td>0.1258</td>
</tr>
<tr>
<td>FOC</td>
<td>2.1 ± 1.5</td>
<td>2.0 ± 1.5</td>
<td>0.0824</td>
</tr>
<tr>
<td>TOTAL MBA Score (Mean)</td>
<td>53.0 ± 14.5</td>
<td>45.6 ± 13.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CSS = Combined Severity Score
FOC = Frontal Occipital Circumference
MBA = Motor Behavioral Assessment
<table>
<thead>
<tr>
<th>Treatment</th>
<th>No History Seizures (n)</th>
<th>History of Seizures (n)</th>
<th>Total CSS</th>
<th>Total MBA Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>208</td>
<td></td>
<td>20.2+/-6.5</td>
<td>45.4+/- 3.8</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>24</td>
<td>22.3+/-7.2</td>
<td>50.2+/- 5.4</td>
</tr>
<tr>
<td>Any Medication</td>
<td>330</td>
<td></td>
<td>25.4+/-7.7</td>
<td>53.0+/- 4.3</td>
</tr>
<tr>
<td>VNS</td>
<td></td>
<td>22</td>
<td>27.1+/-6.9</td>
<td>59.0+/- 2.9</td>
</tr>
<tr>
<td>Ketogenic Diet</td>
<td></td>
<td>21</td>
<td>28.9+/-8.2</td>
<td>58.9+/- 4.1</td>
</tr>
</tbody>
</table>

VNS = Vagus Nerve Stimulator  
CSS = Combined Severity Score  
MBA = Motor Behavioral Assessment
Seizures: Generalized

- Tonic-Clonic
- Clonic
- Tonic
- Atonic
- Myoclonic
- Absence
Seizures: Partial

- Complex Symptomatology
- Elementary Symptomatology
Status Epilepticus

- Seizure Activity Lasts Longer Than 30 Min
- Or, Repeated Seizures Without Return to Baseline Level of Consciousness
- Convulsive vs. Non-Convulsive
Rett Syndrome: EEG

**Awake**

**NREM Sleep**

- F1C3
- F2C4
- C3O1
- C4O2
- F7T3
- F8T4
Rett Syndrome: Seizures

CAUTION!

- Not all Twitching, Stiffening, Staring Events are Seizures
- The EEG is Abnormal in Rett Syndrome, but this Doesn’t Mean the Girl is Having a Seizure
- Video-EEG Monitoring May Be Necessary to Make Appropriate Decisions for Treatment
Rett Syndrome: Non-Seizure Events

- Breath-holding/Hyperventilation
- “Vacant” Episodes with Absence-like Freezing
- Screaming/Laughter
- Stiffening
- Tremulousness
- Falling Forward
- Pupil Dilatation
Rett Syndrome: Non-Seizure Events: Causes

- Motor Dysfunction
- GI: Gastro-esophageal Reflux
- “Rett Behaviors”
- Autonomic Dysfunction
Seizures: Treatment

- None
- Medication
  - Status Epilepticus
  - Clusters of Seizures
  - Vagus Nerve Stimulator
  - Ketogenic Diet
Treatment Goals

- **Efficacy:** No Seizures
- **Safety/Tolerability:** No Side Effects
- **Monotherapy**
- **Most Effective, Easy-to-Follow Regimen**
Antiepileptic Drugs: “Old”

- carbamazepine (Tegretol; Carbatrol)
- clonazepam (Klonopin)
- clorazepate (Tranxene)
- valproate (Depakene; Depakote)
- ethosuximide (Zarontin)
- Phenobarbital
- phenytoin (Dilantin)
- primidone (Mysoline)
AEDs: “Old New”

- felbamate (Felbatol)
- gabapentin (Neurontin)
- lamotrigine (Lamictal)
- oxcarbazepine (Trileptal)
- tiagabine (Gabitril)
- topiramate (Topamax)
AEDs: “New”

- lacosamide (Vimpat)
- levetiracetam (Keppra)
- pregabalin (Lyrica)
- rufinamide (Banzel)
- vigabatrin (Sabril)
- zonisamide (Zonegran)
AEDs: Specialized Use

- lorazepam (Ativan)
- acetazolamide (Diamox)
- Diazepam rectal gel (Diastat Acudial)
AEDs: Side Effects

• “Allergic”: Rash
• GI: Vomiting; Weight Loss or Gain
• Motor: Walking Problems; Tremor
• Sedation: Sleepy
• Behavior: Irritability; Moodiness
• Cognitive: Decreased alertness, communication
Seizures: Treatment

- None
- Medication
- Status Epilepticus
- Clusters of Seizures
- Vagus Nerve Stimulator
- Ketogenic Diet
Seizures: Rx for Clusters

- Rectal Diazepam (Diastat ®)
- Rapid, Reliable Absorption
- Pediatric and Adult Delivery Systems (Plastic Applicator)
- Dose: 2-5 Years, 0.5 mg/kg
  6-11 Years, 0.3 mg/kg
  2 and older, 0.2 mg/kg
Seizures: Treatment

- None
- Medication
- Status Epilepticus
- Clusters of Seizures
- Vagus Nerve Stimulator
- Ketogenic Diet
VAGUS NERVE STIMULATOR
Seizures: Ketogenic Diet

- Very Strict; Fat to Carbohydrate Ratio 4:1 or 3:1
- Sugar-Free Supplements of Multivitamins and Calcium; Antibiotics, Toothpaste, etc.
- Alternative: Medium Chain Triglyceride Oil
Ketogenic Diet: Side EFFECTS

- Reduction Bone Mass
- High Cholesterol
- Renal Stones
- Low Blood Sugar
- Hair Loss
- (Poor Weight Gain)
Rett Syndrome: Seizures

- If seizure free for 2-3 years, discuss tapering and stopping AEDs.
Where Won’t a Cat Sleep?
Rett Syndrome: Seizures

WHAT WE HAVE LEARNED FROM THE NATURAL HISTORY STUDY
Rett Syndrome and Sleep Problems

- >80% have sleep problems
- 29.6% Problems Going to Sleep
- 43.6% Frequent Awakenings
- 18.3% Difficulty Waking up
WHAT ARE THE TYPICAL SLEEP PROBLEMS?

• Insomnia: Difficulty Going and Staying Asleep; Early Morning Awakenings
WHAT ARE THE TYPICAL SLEEP PROBLEMS?

• Wake/Sleep Scheduling
  Delayed Sleep Onset; Early AM Awakenings; Irregular Schedules
WHAT ARE THE TYPICAL SLEEP PROBLEMS?

• Sleep Disordered Breathing
  Obstructive Sleep Apnea
  Central sleep apnea
Part 1

• Treat Medical Problems
• Manage Daytime Behavioral Problems
• Review and Change Medicines as Needed
• Give Information and Make Reasonable Goals
HOW DO YOU MANAGE SLEEP PROBLEMS OF CHILDREN?

Part 2

• Treat Sleep Problems (OSA)
• Sleep Hygiene
• Behavioral Approaches
• Medicines
TOOLS For Evaluation of SLEEP

- Questionnaire
- Sleep Diary
- Actigraphy

**B** = Bedtime problems

**E** = Excessive daytime sleepiness

**A** = Awakenings during the night

**R** = Regularity and duration of sleep

**S** = Snoring
Pediatric Polysomnography

EEG

EOG

Nasal EtCO2

Chin EMG (2)

Nasal Oral Airflow

Microphone

Sao2

Leg EMG (2)

EKG

Respiratory Effort

Tech Observer

Documents arousals, parasomnias, abnormal sleeping position, and attends to any technical problem

Courtesy of Dr. Carol Rosen

Video Camera

Record behavior
Indications for PSG in children

- Suspected OSA
- Titrate CPAP
- Day Time Sleepiness
- Suspected Seizures/Injurious Nocturnal Spells
- Suspected PLMs
MANAGING SLEEP PROBLEMS

- Insomnia
- Sleep Hygiene
- Behavioral interventions
- Medications-Hypnotics
- Sleep Disordered Breathing
  - T & A (tonsils and adenoids)
- CPAP
SLEEP HYGIENE

1. Age/Developmental Appropriate
2. Routine 20-30 Minutes Prior to Bedtime
3. Put to Bed Awake but Drowsy
4. Regular Bedtimes and Nap Times
5. Bedroom: Dark; Cool (<75 F); Safe; Electronic Media Free (only for sleep)
SLEEP HYGIENE

6. Pre-Bedtime Meal: Light Snack
7. No Caffeine/Alcohol
8. Routine Exercise: 3-4 Hours Prior to Bedtime
9. Light: Bright light in AM Promotes Earlier Onset Sleep; PM Bright Light Delays Onset Sleep
Behavioral Treatments

• Extinction
• Graduated Extinction
• Extinction with Parental Presence
• Scheduled Awakenings
Behavioral Treatments

• Parent Education
• Relaxation: Massage Therapy
• Sleep Restriction
PHARMACOLOGIC RX FOR CHILDREN WITH SLEEP PROBLEMS

• No Approved Medicines for Sleep
• Few or No Studies of Kinetics; Safety; Efficacy of Drugs
• Medicines Frequently Used
MEDICATIONS USED FOR SLEEP PROBLEMS OF CHILDREN

• Alpha Agonists: Clonidine (0.025-0.3 mg)
• Hypnotics: Zolpidem (5-10 mg; CR 6.25-11.5 mg); Eszopiclone (2 mg); Ramelteon (8Mg)
• Antidepressant: Trazodone (25-50 mg)
• Melatonin (0.3/2.5-5/25 mg; CR 3 mg)
• Risperidone (0.5 mg HS/0.5mg BID)
THANK YOU AND A GOOD NIGHT SLEEP TO ALL