Co-Morbidities in Dravet Syndrome

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Disclosures

- Zogenix
- Turing Pharmaceuticals
- Colorado Department of Public Health and Environment

There are no conflicts relevant to today’s talk
Objectives

• Review of the Literature

• Results of Qualitative Interview Study

• Results of Survey
  ▪ Sleep
  ▪ Growth
  ▪ Appetite
Themes I Hear In Clinic

- Constipation provokes seizures
- Poor sleep
- Long duration to eat
- Ambulation concerns
- No response to pain
  - Leads to injuries

- Autonomic symptoms
  - Flushing, not tolerating heat/cold
  - Racing HR

- Behavior
  - Perseveration
  - Safety
Literature

- Limited!!

- Gait
  - Crouched gait
    - No children under 6 years
    - ½ Of children 6-12 yr
    - 8/9 of children > 13yr
  - Crouched gait is associated with mobility issues

- Mild Parkinsonian symptoms in 11/12 adults
  - Bradykinesia
  - Rigidity
  - Cogwheeling

R odda, 2012
Rilestone, 2012
Fasano, 2014
Literature

- **Endocrine**
  - No literature

- **Sleep**
  - 6 children → no abnormalities!!!

- **GI issues**
  - No literature

- **Pain**
  - No literature

- **Autonomic symptoms**
  - No literature

Dhamija, 2014
Literature

• Cognition
  ▪ Decreases over time
  ▪ No correlation between
    • Age at seizure onset
    • Status epilepticus
    • Number of seizures
    • Myoclonus or absence seizures

• Behavior
  ▪ Attention problems
  ▪ Impulsiveness
  ▪ Perseverative responses
  ▪ Deficits in planning
Interviews

• Interviewed 10 families
  ▪ 5 Colorado Hospital Colorado
  ▪ 5 Lurie Children’s Hospital

• Recorded interviews

• Across the age span

• Describe:
  ▪ Associated symptoms
  ▪ How it affects life (now and in the future)
  ▪ How do you cope
  ▪ What do you think causes this
Sleep

- Difficulty getting to sleep
- Frequent awakenings
- Can lead to parental sleep disruption
- Co-sleeping (for sleep and seizure safety)
- Children are sleeping during the day because of night time seizures
- Sleep apnea – some treated surgically
- Parents are fearful at night due to SUDEP
Constipation

- Large stools
- Infrequent stools
- Requires treatment: regular medications and emergency treatment
- May be associated with seizures
- “mega colon”
- Medication leads to loose stools
Appetite

- Mixed themes
  - Some very good eaters
  - Others very limited
- Difficulty chewing
- Choking
- Decreased appetite
- Food fads
- Increased duration of mealtime (2 hours!)
- Required supplementation with g tube
Appetite Coping Strategies

- Using timers
- Providing assistance to reduce time
- Siblings may help to encourage

“Eat a variety of foods but he becomes obsessive over certain foods. … Right now its cheese quesadillas and guacamole, but he’s wants that every day. But, at the same time he wants that every day but he’ll still eat other things that you offer”
Response to Pain

• Several children with lack of response to pain led to injury –
  ▪ AFO causing blisters
  ▪ Self extubation
  ▪ Touching hot objects

• No problems with blood draws

“Do you have any concerns about how __ experiences pain?
R: yeah, he, he doesn’t.”
Dental

• Delayed eruption of teeth (by several years)

• Some gum hyperplasia
  - Attributed to medications
Autonomic Symptoms

- Universal lack of sweating
- Not just that change in temp leads to seizures, also don’t regulate temperature well
  - can’t cool down
  - turns red in heat
- Cold hands and feet
- Families may treat overheating with ibuprofen
- Avoid activities due to overheating
- Avoid bathing due to change in temp -> seizure
Enjoyed Activities

- Busy kids “doesn’t sit still for long”
- Puzzles
- Focus on same movie or TV shows
- Riding bikes
- “Keeping busy”
- Water
- Bubbles
- Seeking interactions with other children but better with adult
How are Activities Limited?

- “25% of the time had to stop”
- Stop for temperature and seizures
- Limits normal kid things
- Decreased stamina
- Not able to hike, use strollers
- Requires help to do many activities
- Not able to go to restaurants – too long to eat
- Limit activities due to illness
- Miss family activities if someone else is sick
- Avoid parks, play ground, children’s museum – places with increased risk of infection
Friends and Family

• Hard for others to understand concerns and limitations

• “Maybe very hard for them to understand truly what the needs are there”

• Hard to attend events for friends and family – may take turns or avoid all together

• “like you’re damned if you do and you’re damned if you don’t.”

• Need to make exceptions

• Parents (grandparents) help when live close by – seem to understand more

• “I think one of the things that we find is that people are intimidated”
Perception Of Child’s Feelings

• Overall happy content kids

• Not much frustration or awareness of seizures

• Frustration comes from not being able to do things –
  ▪ Attributed to fatigue, balance, inability to run
Parental Feelings

• Sadness

• Worry

• Worry about things getting worse

• “The syndrome itself really impacts, not just him the entire family.”

• “this just happens to be a challenge for all . . . the challenge for all of us.”
SURVEY
Surveys To Assess Co-morbidities

- Survey caregivers of children with Dravet Syndrome
- Sent via DSF email list
- 5-10 minutes to complete
Survey Questions

How much do you agree or disagree with the following statements about your child's eating habits (over the last 2 months)?
(If your child is fed only through a feeding tube, please select "does not apply")

<table>
<thead>
<tr>
<th></th>
<th>strongly agree</th>
<th>agree</th>
<th>disagree</th>
<th>strongly disagree</th>
<th>does not apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>4) My child has a good appetite most of the time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5) My child eats a variety of foods</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6) My child finishes a meal in the same amount of time as other children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Survey Respondents

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of respondents</td>
<td>202</td>
</tr>
<tr>
<td>Age – mean (range)</td>
<td>8 (5,14)</td>
</tr>
<tr>
<td>Male</td>
<td>101 (50%)</td>
</tr>
<tr>
<td>Known SCN1A mutation</td>
<td>182 (90.5%)</td>
</tr>
<tr>
<td>Relationship of respondent - parent</td>
<td>162 (95.9%)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>16 (9.5%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>&lt; high school</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>College grad and more</td>
<td>115 (68.5%)</td>
</tr>
<tr>
<td>Marital status - married</td>
<td>138 (82.1%)</td>
</tr>
</tbody>
</table>
### GI Symptoms

<table>
<thead>
<tr>
<th>Feeding Concerns</th>
<th>N</th>
<th>%</th>
<th>% Poor Appetite</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor appetite</td>
<td>182</td>
<td>35.7%</td>
<td>-</td>
<td>9.3</td>
<td>4.4-19.5</td>
<td>5.2 (2.4-11.7)</td>
</tr>
<tr>
<td>Decreased variety of food</td>
<td>177</td>
<td>49.7%</td>
<td>59.1%</td>
<td>9.3</td>
<td>4.4-19.5</td>
<td>5.2 (2.4-11.7)</td>
</tr>
<tr>
<td>Prolonged meal times</td>
<td>173</td>
<td>68.2%</td>
<td>47.5%</td>
<td>7.4</td>
<td>2.9-18.5</td>
<td>3.9 (1.4-10.6)</td>
</tr>
<tr>
<td>Assistance with feeding</td>
<td>172</td>
<td>34.3%</td>
<td>56.9%</td>
<td>3.5</td>
<td>1.8-6.8</td>
<td>2.6 (1.2-5.8)</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>175</td>
<td>28.6%</td>
<td>45.8%</td>
<td>1.7</td>
<td>0.8-3.3</td>
<td></td>
</tr>
<tr>
<td>Difficulty chewing</td>
<td>174</td>
<td>41.4%</td>
<td>43.1%</td>
<td>1.6</td>
<td>0.8-3.0</td>
<td></td>
</tr>
<tr>
<td>Food fads</td>
<td>174</td>
<td>67.8%</td>
<td>44.9%</td>
<td>3.0</td>
<td>1.4-6.2</td>
<td></td>
</tr>
<tr>
<td>Picky eater</td>
<td>174</td>
<td>66.1%</td>
<td>47.8%</td>
<td>4.5</td>
<td>2.1-9.7</td>
<td></td>
</tr>
</tbody>
</table>
# Sleep in Dravet Syndrome

<table>
<thead>
<tr>
<th>Sleep Issues</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any sleep problem</td>
<td>179</td>
<td>82.1%</td>
</tr>
<tr>
<td>Apnea</td>
<td>179</td>
<td>31.3%</td>
</tr>
<tr>
<td>Difficulty falling asleep</td>
<td>179</td>
<td>64.8%</td>
</tr>
<tr>
<td>Awakens from sleep</td>
<td>179</td>
<td>69.3%</td>
</tr>
<tr>
<td>Short time of sleep</td>
<td>179</td>
<td>52.5%</td>
</tr>
</tbody>
</table>

Sleep in Dravet Syndrome
## Other Reported Symptoms

<table>
<thead>
<tr>
<th>Other reported symptoms</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooping causes seizures</td>
<td>179</td>
<td>21.2%</td>
</tr>
<tr>
<td>Unable to tolerate cold</td>
<td>179</td>
<td>55.3%</td>
</tr>
<tr>
<td>Hands turn blue</td>
<td>179</td>
<td>36.3%</td>
</tr>
<tr>
<td>Frequent falls</td>
<td>179</td>
<td>70.4%</td>
</tr>
<tr>
<td>Avoid stairs</td>
<td>179</td>
<td>33.5%</td>
</tr>
<tr>
<td>Balance problems with change of surfaces</td>
<td>179</td>
<td>75.4%</td>
</tr>
<tr>
<td>Little response to pain</td>
<td>179</td>
<td>76.0%</td>
</tr>
<tr>
<td>Doesn’t report injuries</td>
<td>169</td>
<td>61.0%</td>
</tr>
<tr>
<td>Frequent illness</td>
<td>179</td>
<td>69.8%</td>
</tr>
<tr>
<td>Prefers to play with adults</td>
<td>169</td>
<td>65.1%</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>169</td>
<td>24.9%</td>
</tr>
<tr>
<td>Short stature</td>
<td>169</td>
<td>36.7%</td>
</tr>
<tr>
<td>Lighter skin</td>
<td>169</td>
<td>34.3%</td>
</tr>
</tbody>
</table>
GROWTH AND ENDOCRINE
Data Collection

• Retrospective chart review
  ▪ Height
  ▪ Weight
  ▪ Medications
    • Current
    • Prior
  ▪ Endocrine testing
  ▪ Family history of endocrine testing
<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years – mean (SD)</td>
<td>9.9 (5.5)</td>
</tr>
<tr>
<td>Male</td>
<td>46%</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>18%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>72.1%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>4.4%</td>
</tr>
<tr>
<td>Other</td>
<td>23.4%</td>
</tr>
<tr>
<td>Health Insurance*</td>
<td></td>
</tr>
<tr>
<td>Medicaid / CICP</td>
<td>83.8%</td>
</tr>
<tr>
<td>Private</td>
<td>38.2%</td>
</tr>
<tr>
<td>Tricare</td>
<td>4.4%</td>
</tr>
<tr>
<td>Anti-seizure meds</td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>38%</td>
</tr>
<tr>
<td>≥3-7</td>
<td>62%</td>
</tr>
</tbody>
</table>
## Endocrine Abnormalities

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Subjects with an abnormal result / Total # tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1</td>
<td>6 / 14</td>
</tr>
<tr>
<td>TSH</td>
<td>2 / 23</td>
</tr>
<tr>
<td>Sex hormones</td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>2 / 6</td>
</tr>
<tr>
<td>LH</td>
<td>1 / 6</td>
</tr>
<tr>
<td>Estradiol</td>
<td>0 / 1</td>
</tr>
<tr>
<td>Testosterone</td>
<td>3 / 10</td>
</tr>
<tr>
<td>Cortisol</td>
<td>2 / 8</td>
</tr>
</tbody>
</table>
Endocrine Abnormalities

• 2 children with IGF-1 abnormalities had additional testing to confirm growth hormone deficiency

• One child had complete pituitary dysfunction
  ▪ thyroid problems
  ▪ cortisol problems

• Two children treated with testosterone
**Weight Compared To Norms**

Weight Z-score of Children with Dravet Syndrome

*Predicted means are calculated from a mixed linear regression model with a random intercept and slope.*
Height Compared To Norms

Height Z-score of Children with Dravet Syndrome

*Predicted means are calculated from a mixed linear regression model with a random intercept and slope.
Height and Weight

• Over time height and weight fall below the expected average for the US population

• Height falls off before weight

• With poor nutrition – weight falls off before height – what we are seeing is not nutrition

• So why does this happen?
  ▪ Genetics
  ▪ Endocrine dysfunction
  ▪ Medications
Putting It All Together

• Dravet Syndrome is more than seizures and cognition
• Many of these associated symptoms likely affect quality of life
  ▪ Sleep
  ▪ Appetite
  ▪ Gait
  ▪ Behavior
• More research to identify best management in these areas