Saturday, August 3, 2019
Breakout Session A2 • 10:45-11:45am • Grand Ballroom C

Gastrointestinal Issues in CHARGE Syndrome
Does Your Gut Talk to You?

Dr. Kim Blake, IWK Health Centre

Presenter Information
Dr. Kim Blake is a professor of pediatrics at Dalhousie University in Nova Scotia, Canada. She has been researching in CHARGE syndrome over the last 35 years and has published extensively. She has explored post-operative airway events, sleep apnea, bone health, cranial nerve abnormalities, and gastrointestinal issues. In the last 10 years Dr. Blake has partnered with Dr. Jason Berman and they have developed a zebra fish model of CHARGE syndrome to answer further research questions. With this model we have been able to understand about the abnormalities of the vagus nerve and gut mobility in CHARGE syndrome which has influenced our knowledge of gut motility. Anesthesia and sedation risk has also been researched in our zebra fish model. This supports the clinical findings that individuals with CHARGE syndrome have increased risk following anesthesia and should have combined procedures where possible in one anesthesia. Kim is very proud of the CHARGE syndrome checklist which has been developed both for families, individuals, and professionals to use as a guide and a teaching tool for anybody dealing with CHARGE syndrome.

Presentation Abstract
Review of Gastrointestinal (GI) motility and the connection to the vagus nerve and microbiome in CHARGE syndrome. Gastrointestinal (GI) dysfunction including feeding, and digestion difficulties are highly prevalent and represent a serious challenge for many individuals with CHARGE syndrome. We are much further along the journey in understanding the GI tract which is the largest organ of the body and deserves more attention. In this presentation we will summarize in an easy digestible format the knowledge to date; this will help you understand and advocate for the gut in CHARGE. We are excited in sharing with you the research undertaken by the Atlantic Canadian CHARGE syndrome research group. We have been studying the type of bacteria found in the gut called the “Gut microbiome.” We are continuing to recruit for this research at the conference, pop by and see us to learn more.

Learning Objectives
• To understand more about the gastrointestinal (GI) issues faced by individuals with CHARGE syndrome.
• To be an advocated for the CHARGE ‘gut’ and have the up to date literature at your fingertips to share with your specialist.
• To be knowledgeable about microbiome and how it may be impacted in CHARGE syndrome.
Gastrointestinal issues in CHARGE syndrome: Does your gut talk to you?

Dr. Kim Blake, Professor of Pediatrics
Dalhousie University, Nova Scotia, Canada
kblake@dal.ca
Case History
Objectives

After this presentation you will have a greater understanding of:

1. The breath of gastrointestinal issues in CHARGE syndrome
2. The clinical and basic science research, including our zebra fish model.
3. The provisional results of our microbiome studies

The GI tract goes from mouth to anus
The upper GI tract
Cranial nerve innervations and structural abnormalities are key issues

- Cranial facial abnormalities can interfere with feeding particularly in infancy.
- Children with choanal atresia/ stenosis have significantly more GI symptoms than those without.#
- Excessive salivation secretion can be a problem
- Mouth over stuffing and pocketing is prevalent.*

#Macdonald 2016 AJMG
*Hudson 2016 AJMG
Gastroesophageal Reflux (GER) and tube feeding

- Gastroesophageal Reflux is often severe and difficult to treat.
- Tube feeding is highly prevalent and can be protracted
- Tube feeds vs. oral feeders have more
  - Stomach pain
  - Discomfort when eating
  - Food and drink limits
  - Trouble swallowing
  - Nausea and vomiting
  - Constipation

“Motility issues” are a key problem.

Macdonald 2016 AJMG
Abdominal Pain

- Prevalent and difficult to assess and the underlining diagnosis is often missed.
- Digestion issues are clinically present. There has been very little research in this area.

“The gut is different in CHARGE syndrome”

Hartshorne and Stratton, Research on pain scale
Constipation
How many of you have problems with this?

Prevention:
• Fluids
• Exercise
• Behavioral therapy
• Diet
• Massage

Treatment:
• Polyethylene glycol / MiraLAX
• PEG
• Senocot
• Behavioral techniques
Risk factors for poor bone health in adolescents and adults with CHARGE syndrome.

Key Findings
• 87% of individuals are not getting enough vitamin D
• 41% not getting enough calcium

Recommendations:
• Increase in the amount of calcium and vitamin D
• Replace sex hormones.
• Increase in weight bearing activity
• # 100 iu Vit D
Conditions that are missed and need to be on the differential diagnosis

- Abdominal colic
- Pocketing/Overstuffing
- Gall stones
- Dumping syndrome
Dietary advice that may help digestion issues.

- Reduce simple carbohydrates (Bread, pasta)
- Small amounts of food regularly.
- Exercise and weight control.
- Low FODMAP diets.
Etiology and functional validation of Gastrointestinal motility dysfunction in a zebra fish model of CHARGE syndrome

Loss of chd7 in zebrafish results in:

- Smaller stomachs and GI tracts with normal epithelial and muscular histology.
- Decrease and disorganized vagal nerve projections particularly in the fore gut.
- Less ability to empty their GI tract only minimally improved by pro kinetic agents.

Future

Zebrafish are an excellent model for studying compounds that improve GI motility in individuals with CHARGE syndrome.

International Journal of Pediatric Otorhinolaryngology V82, March 2016, pgs. 107-115
Clooney et al FEEBS 285,11, 2018
Innervation of the CHARGE Zebrafish (chd7) and normal controls in the gut

- Decreased enteric nerve branches around the fore gut (Compare A & B)
- Difference in size and shape of the gut in the CHARGE fish.

Sp = spine, F = ventral fin, V = vent, G = gut (outlined in hashed line), arrow = vagal nerve plexus, y = yolk

Clooney et al FEEBS 285,11, 2018
International Journal of Pediatric Otorhinolaryngology V82, March 2016, pgs. 107-115
Decreased motility shown in CHARGE zebrafish by delayed emptying of GI tract

*Florescent green = tagged food travel. GI tract of zebra fish over time
A feeding scale for CHARGE syndrome

| Date: | | |
| Name of Individual: | | |
| Age: | | |
| Completed By (Circle one): Mother | Father | Feeding Therapist | Name/Physician | Not Disclosed | Other | |

What percentage of your child/adult’s daily fluid/nutrition intake is by GI tube feeding? (Circle one percentage):

- 0% | 25% | 50% | 75% | 100% |

<table>
<thead>
<tr>
<th>Circle one number on the scale:</th>
<th>Never</th>
<th>A Little</th>
<th>Sometimes</th>
<th>A lot</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>He/she will refuse food when eating orally.</td>
<td>0</td>
<td>1</td>
<td>2</td>
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<td>2</td>
<td>He/she takes longer than 15 minutes to eat orally.</td>
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<tr>
<td>3</td>
<td>He/she takes less than 15 minutes to eat orally.</td>
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<td>3</td>
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<td>4</td>
<td>He/she needs close supervision when eating orally.</td>
<td>0</td>
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</tr>
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<td>5</td>
<td>He/she needs someone in the room when eating orally.</td>
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<td>2</td>
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<td>6</td>
<td>He/she has problems cutting food when eating orally.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>7</td>
<td>He/she has problems feeding himself/herself when eating orally.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>8</td>
<td>He/she chokes or coughs when eating orally.</td>
<td>0</td>
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<td>2</td>
<td>3</td>
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<td>9</td>
<td>He/she has trouble chewing food.</td>
<td>0</td>
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<td>2</td>
<td>3</td>
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<tr>
<td>10</td>
<td>He/she has trouble swallowing food.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>11</td>
<td>He/she has to be held or reminded to chew.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>He/she has to be held or reminded to swallow.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>He/she does not like to mix food textures when eating (e.g., mixing puree and solid food).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>He/she accidentally loses food out of his/her mouth during eating.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>He/she will over-stuff his/her mouth with food during eating.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

| 16 | He/she has difficulty moving food around with his/her tongue during eating. | 0 | 1 | 2 | 3 | 4 |
| 17 | He/she has a hard time feeling food or anything touching the inside of his/her mouth. | 0 | 1 | 2 | 3 | 4 |
| 18 | He/she dislikes oral eating. | 0 | 1 | 2 | 3 | 4 |
| 19 | He/she has food sit in his/her cheeks or palate during eating (on purpose or not). | 0 | 1 | 2 | 3 | 4 |
| 20 | He/she will have food hidden in his/her cheeks or palate after the meal has ended (on purpose or not). | 0 | 1 | 2 | 3 | 4 |
| 21 | The Parent/Caregiver gets worried about their child/adult’s ability to eat orally. | 0 | 1 | 2 | 3 | 4 |
| 22 | The Parent/Caregiver has difficulties feeding their child/adult. (e.g., preparing food the right way, getting enough information about helping them eat orally) | 0 | 1 | 2 | 3 | 4 |

Does the child/adult have problems with:

- No | Yes

| 23 | Cold foods | 0 | 1 |
| 24 | Room temperature foods | 0 | 1 |
| 25 | Warm foods | 0 | 1 |
| 26 | Thin liquids (e.g., water) | 0 | 1 |
| 27 | Pureed foods (e.g., applesauce) | 0 | 2 |
| 28 | Mashed food (e.g., mashed potatoes or mashed vegetables) | 0 | 2 |
| 29 | Soft chewable foods (e.g., bread, crackers) | 0 | 2 |
| 30 | Tough chewable foods (e.g., meat) | 0 | 2 |
| 31 | Hard vegetables and fruit (e.g., raw apples) | 0 | 2 |

Total Score (sum of all items) /100 total points

<table>
<thead>
<tr>
<th>Circle one:</th>
<th>Feeding difficulties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (0-25 points)</td>
<td>Moderate (26-50 points)</td>
</tr>
</tbody>
</table>
### Subsection of Feeding Scale

#### Scoring of feeding scale for CHARGE syndrome

**Total Score** (sum of all items) /100 total points

<table>
<thead>
<tr>
<th>Item</th>
<th>Never</th>
<th>A Little</th>
<th>Sometimes</th>
<th>A Lot</th>
<th>Always</th>
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<td>16 He/she has difficulty moving food around with his/her tongue during eating.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17 He/she has a hard time feeling food or anything touching the inside of his/her mouth.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18 He/she dislikes oral eating.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19 He/she lets food sit in his/her cheeks or palate during eating (on purpose or not).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20 He/she will have food hidden in his/her cheeks or palate after the meal has ended (on purpose or not).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>29 Soft chewable foods (e.g. bread, crackers)</td>
<td>0</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 Tough chewable foods (e.g. meat)</td>
<td>0</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31 Hard vegetables and fruit (e.g. raw apples)</td>
<td>0</td>
<td></td>
<td>1</td>
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Out of 100 points
Higher score = worse feeding difficulties
Three uses for the feeding scale for CHARGE Syndrome

1. To assess the severity of feeding difficulties
2. To track oral feeding progress before and after interventions
3. To warn the clinician and feeding therapist of new concerns
GI and feeding difficulties in CHARGE syndrome:
Treatments tried and parents’ perceptions of their effectiveness
Parents’ perceptions of treatments tried for gastrointestinal and feeding issues in CHARGE syndrome

- 31 respondents (Australia, NZ, USA, UK, Sweden, Indonesia)
- 18 males, 13 females with CHARGE syndrome

Top Parent-Reported Issues:
- Reflux
- Excess salivation
- Abdominal pain
- Diminished smell

https://surveys.dal.ca/opinio/s?s=39536
Medications Tried

- **Excess saliva** – Glycopyrolate, Botox
- **Reflux** – Omeprazole, Esomeprazole, Ranitidine, Cisapride
- **Abdominal pain** – Acetaminophen
- **Constipation** – PEG, Osmolax, Coloxyl, Parachoc, Movicol Jr, Domperidone

Surgeries Undergone

- **Aspiration** – G-tube, tracheostomy, tracheoesophageal fistula (TEF) repair
- **Abnormal tongue movement** – frenulectomy
- **Abnormal chewing** – teeth extraction, orthodontics
- **Abnormal swallowing** – esophageal dilatation to treat esophageal stenosis
- **Reflux** – Nissen fundoplication
- **Abdominal pain** - laparoscopic investigations, emergency laparotomy for bowel obstructions
Behavioral Therapy Tried

- **Excess salivation** – Speech Language Therapy (SLT), suctioning, swallowing reminders, vital stim therapy
- **Aspiration** – limit certain foods/liquids, SLT, close supervision
- **Pocketing of food in cheeks, Overstuffing, Abnormal tongue movements, Abnormal swallow/chew** – Prompting while eating, SLT, dissolvable foods, eating with the family at mealtime
- **Reflux** – Tilt the head of the bed up, remain upright after eating
- **Abdominal pain** – Dairy-free diet, abdominal massage, warm baths, fibre
- **Constipation** – Exercise
- **Overweight** – more emphasis on whole foods and less processed foods
Treatments That Parents Think are LEAST Effective

- **Excess saliva** – Constant suctioning
- **Abdominal pain** – Acetaminophen
- **Constipation** – Movicol Jr, lactulose
- **Reflux** – Changing formula types

Treatments That Parents Think are MOST Effective

- **Excess saliva, Aspiration** – Being vertical, SLT, vitalstim therapy, botox
- **Pocketing of food, Over-stuffing, Abnormal sensation in mouth** – SLT, eating with family
- **Abnormal chewing** – Orthodontics, behavioral therapy
- **Reflux** – Fundoplication, medication
- **Abdominal pain** – Increased fibre, abdominal massage, warm baths
- **Constipation** – Less junk food, parachoc
Members of the Treatment Teams

- Pediatrician
- Family physician
- Pulmonologist
- Gastroenterologist
- ENT surgeon
- General surgeon
- Physiatrist/Rehabilitation physician
- Speech language pathologist
- Occupational therapist
- Physical therapist
- Massage therapist
- Dentist
- Dietician
Microbiome

Background

• Food travels from mouth to anus through the gastrointestinal tract (GI tract)
• Food is digested and excreted along the way by chemicals and precise movements in the GI tract

BUT... there are also trillions of bacteria and other organisms that help keep our guts healthy = GUT MICROBIOME

Gut dysbiosis

Typical microbiome contains:
- Firmicutes
  - Actinobacteria
- Bacteroidetes
- Proteobacteria

When these change in type or number and cause GI distress → dysbiosis

Gut dysbiosis is associated with GI disorders and extra-intestinal disorders:
- Crohn’s/Colitis
- Irritable bowel syndrome
- Obesity
- Autism
- Etc....
Research Question

1) Does the gut microbiome differ in individuals with CHARGE syndrome compared to individuals who are not affected with CHARGE?

2) If so, does the change in gut microbiome correlate with the severity of GI symptoms?

3) And does the change in gut microbiome correlate with dietary factors?

Study Design

Participants: Individuals with CHARGE syndrome from the Canadian Maritimes and if possible, their sibling who is unaffected by CHARGE

- 7 individuals with CHARGE (proband)
- 4 sibling controls (subject)

Each participant provided:

- a stool sample
- a Block Food Screener
- a PedsQL GI symptom severity questionnaire
PEDSQL
GASTROINTESTINAL SYMPTOM SCALE

Rate the following from 0 (never) – 4 (almost always)
➢ stomach pain
➢ stomach discomfort when eating
➢ food and drink limits
➢ trouble swallowing
➢ heartburn and reflux
➢ nausea and vomiting
➢ gas and bloating
➢ constipation
➢ diarrhea
➢ blood in bowel

Results and Discussion
In progress
What’s next?

Limitations:

- Small study size: hard to make inferences since the gut microbiome is highly variable
- Lack of control subjects for all participants with CHARGE

Future Study:

- Repeat study with more participants
- Include parents to participate as matched control

INTERESTED IN HELPING?
Come visit us!
Study can be completed at the conference
OR
We provide you with mailing material
**CHARGE Syndrome Checklist: Health Supervision Across the Lifespan**

**From Head to Toe**

<table>
<thead>
<tr>
<th>Description</th>
<th>Infancy (0-2 years)</th>
<th>Childhood (3-5 years)</th>
<th>Adolescence (13-17 years)</th>
<th>Adulthood (18+ years)</th>
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<tbody>
<tr>
<td>1. Head growth: Head size is about 2 inches less than normal head size.</td>
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<td>2. Eye contact:</td>
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<td>3. Central nervous system problems: Monitor for absent non-rigidity, hypotonia, and slow development.</td>
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<td>5. Growth velocity:</td>
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**Central Nervous System**

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<td>3. Central nervous system problems:</td>
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<td>4. Congenital heart defects:</td>
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<td>5. Growth velocity:</td>
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**Growth Velocity**

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**Developmental**

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**Medical History**

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**Physical Examination**

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**Conclusion:**

- Consider neurodevelopmental evaluation.
- Consider referral for pediatric neurology or genetics.

**IWK CHARGE Clinic**

Students & Residents Using the CHARGE Checklist
Questions and Answers