Gastrointestinal (GI) and Feeding Difficulties in CHARGE Syndrome; the Guts of It
Kim Blake, MD, Professor, Dalhousie University

Presenter Information
Dr. Kim Blake is a professor of pediatrics at Dalhousie University in Nova Scotia, Canada. She has been researching 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 zebrafish 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 zebrafish 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
The aim of this presentation is to discuss the gastrointestinal (GI) symptoms and feeding difficulties in CHARGE syndrome.

Over 95% of individuals with CHARGE syndrome experience feeding and gastrointestinal (GI) dysfunction. The structural abnormalities, motility impairment and sensory impairment all contribute to the GI issues and are potential treatment targets. I will describe how cranial nerve abnormalities underlines the pervasive GI dysfunction and the need for further research on gut motility and the microbiome. Much of the work has come from Dr. Blake’s laboratory/team at Dalhousie University in Canada. She will describe the clinical and basic science research that has been completed over the last 10 years. A recent publication titled “Etiology and functional validation of gastrointestinal motility dysfunction in a zebrafish model of CHARGE syndrome” will be discussed. Dr. Blake will also touch on the microbiome and preliminary data from her students.

Learning Objectives
• To leave you more knowledgeable and inspire you to ask questions about the forgotten gastrointestinal (GI) issues in CHARGE syndrome.
• To share with you and your family the CHARGE syndrome checklist (Trider et al 2017) and the feeding assessment scale (Hudson et al).
• To be an advocate for the CHARGE “gut” and move the research forward in gut motility and the microbiome.
Gastrointestinal (GI) and feeding difficulties in CHARGE syndrome; the guts of it.

Dr. Kim Blake, Professor of Pediatrics
Dalhousie University, Nova Scotia, Canada
kblake@dal.ca  http://www.drkimblake.com
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http://www.drkimblake.com
Dr. Blake’s virtual lab

http://www.drkimblake.com

IWK Health Centre 2019
The gut is different in CHARGE syndrome

Gastrointestinal (GI) issues arise from
• Structural abnormalities
• Motility impairment
• Sensory impairment

These are all potential targets for treatment
Gastrointestinal and feeding difficulties in CHARGE syndrome: A review from head-to-toe

http://www.drkimBlake.com
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 then those without.#
• Excessive salivation secretion can be a problem
• Mouth over stuffing and pocketing is prevalent.*

#Macdonald et al 2016
AJMG
*Hudson et al 2016 AJMG

http://www.drkimblake.com
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 et al 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”

Hartsthorn and Straton, 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 (motility agents)
• 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
• # 1000 iu Vit D

Forward 2007 AJMG
Conditions that are missed and need to be on the differential diagnosis

- Abdominal colic
- Pocketing/Overstuffing
- Gall stones
- Dumping syndrome
# IWK CHARGE Clinic

## Students & Residents Using the CHARGE Checklist

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### CHARGE SYNDROME CHECKLIST: HEALTH SUPERVISION ACROSS THE LIFESPAN

**FROM HEAD TO TOE**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Infant (0-1 mo)</th>
<th>Childhood (2-11 yr)</th>
<th>Adolescence (12-18 yr)</th>
<th>Young Adult (19-30 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
</tr>
<tr>
<td>Ocular</td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
</tr>
<tr>
<td>Craniofacial</td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
</tr>
<tr>
<td>Neurological</td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
</tr>
<tr>
<td>Endocrine</td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
</tr>
</tbody>
</table>

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**Additional notes:**

- **+** indicates a normal finding.
- **-** indicates a finding of concern.
- **0** indicates no finding.

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**References:**

- [http://www.drkimblake.com](http://www.drkimblake.com)

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**Image:**

- Photograph of students and residents using the CHARGE checklist.

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**Contact:**

- Dr. Kim Blake
- [http://www.drkimblake.com](http://www.drkimblake.com)
A feeding scale for CHARGE syndrome

<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. Hushe will refuse food when eating orally.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Hushe takes longer than 45 minutes to eat orally.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Hushe takes less than 15 minutes to eat orally.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Hushe needs close supervision when eating orally.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Hushe needs someone in the room when eating orally.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Hushe has problems cutting food when eating orally.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Hushe has problems feeding himself when eating orally.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Hushe chokes or coughs when eating orally.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Hushe has trouble chewing food.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Hushe has trouble swallowing food.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Hushe has to be held or reminded to chew.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Hushe has to be held or reminded to swallow.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Hushe does not like tasty food textures when eating (e.g., mixing puree and solid food).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Hushe accidentally loses food out of his/her mouth during eating.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Hushe will over-stuff his/her mouth with food during eating.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Does the child/his have problems with:</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Cold foods</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>24. Roors temperature foods</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>25. Warm foods</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>26. Thin liquids (e.g. water)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>27. Pureed foods (e.g. applesauce)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>28. Smooth thick food (e.g. mashed potato or mashed vegetables)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>29. Soft chewable foods (e.g. bread, crackers)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>30. Thick chewable foods (e.g. meat)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>31. Hard vegetables and fruit (e.g. raw apples)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Score (sum of all items)</th>
<th>/100 total points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circle one:</td>
<td>Feeding difficulties: Mild (0-25 points), Moderate (26-50 points), Severe (51-100 points)</td>
</tr>
</tbody>
</table>
Subsection of Feeding Scale

Scoring of feeding scale for CHARGE syndrome

Out of 100 points
Higher score = worse feeding difficulties

http://www.drkimblake.com
The feeding scale for CHARGE Syndrome; used to

1. Assess the severity of feeding difficulties
2. Track oral feeding progress before and after interventions
3. Warn the clinician and feeding therapist of new concerns
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.

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 zeba fish over time
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 CHARGE 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

Emily Chedrawe Research Student Dalhousie University
Provisional Results

N = 11
- CHARGE n=7
- Control n=4

Figure 1: Average relative abundance of bacteria phyla found in the gut microbiome of individuals with CHARGE (blue) and sibling control (red)

No significant differences
Comparing one sibling pair with different GI scores

The sibling with CHARGE had moderate feeding difficulties according to PASSFP; the control sibling had no feeding difficulties.
Comparing one sibling pair with similar GI scores

The sibling pair scored within low range of feeding difficult and GI symptoms for the PASSFP and PEDSQL questionnaires.
Discussion and Conclusion

• The CHARGE microbiome is different in our provisional results

• Trend: ↑ Bacteroidetes  ↓ Firmicutes and ↓ diversity
  • Bacteroidetes are important for maintaining a healthy gut, regulating the immune system and the gut-brain axis
  • Firmicutes ferment carbohydrates in the gut. Decrease also seen in IBD.
  • Decreased diversity is also seen in IBD, IBS, obesity and autism and is related to increased susceptibility to diseases

• Next steps: increase study population, compare microbiome according to feeding types and specific GI symptoms, use software to assess functional impact of the altered bacteria
Novel Therapies for dysbiosis: Fecal Transplantation

• Stool from a healthy donor → screening → transplant to patient
• Some formulas are being made in labs instead of needing donor
• Transplant can be per rectum or orally
• Found effective in C. difficile infection and IBD
• Risks include transmission of infection missed during screening and risks associated with colonoscopy
Questions and Answers