

Kim Blake

21st June 2024

***„The guts of it: CHARGE syndrome
and the gastrointestinal tract”***



The guts of it: CHARGE Syndrome, and the gastrointestinal tract



June 19th – 23rd, 2024

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CHARGE
CHARGE Syndrome e.V.

Oberwesel
Germany



www.drkimblake.com

Objectives

This presentation will give you an update on the GI findings in CHARGE syndrome

- I will share the Abdominal migraine and constipation pamphlets that have been developed for families and professionals
- You will have a better understanding of the microbiome issues in CHARGE syndrome
- You will gain knowledge on the more complex and serious issues that can develop in the GI system
- QR code for pamphlets

CHARGE CHECKLIST: HEALTH SUPERVISION ACROSS THE LIFESPAN

- Key assessment/reassessment points across the lifespan
- Supports all care providers to manage patients with CHARGE Syndrome

CHARGE Syndrome Checklist: Health Supervision Across The Lifespan (Printable PDF)

Category	Item	0-3	3-5	5-10	10-18	18+
Developmental/Behavioral	Developmental milestones					
	Communication skills					
	Autism spectrum disorder					
	Attention deficit hyperactivity disorder					
	Intellectual disability					
	Seizures					
	Abuse/neglect					
	Substance use					
	Depression					
	Chronic pain					
Medical	Cardiovascular					
	Respiratory					
	Renal					
	Endocrine					
	Neurological					
	Orthopedic					
	Genetic					
	Immunology					
	Reproductive					
	Other					



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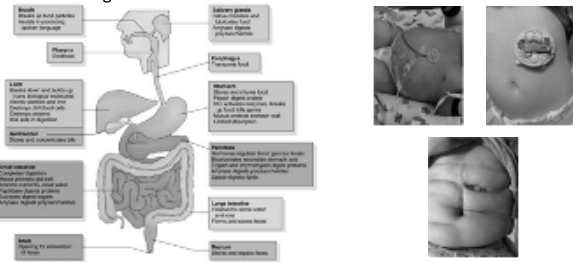
CHARGE Clinical Checklist

Gastroenterology Genitourinary

GASTROENTEROLOGY GENITOURINARY	Gastroesophageal reflux – Gastroenterology consult – consider mobility agents with proton pump inhibitor		
	Poor suck/chew/swallow - feeding team assessment/intervention		
	Aspiration risk, tracheoesophageal fistula – swallowing studies		
	May need supplemental feeds – frequently requires gastrostomy tube or gastrojejunostomy tube		
	Constipation – consider Senna glycoside with polyethylene glycol		
	Renal anomalies – abdominal u/s +/- VCUG, blood pressure monitoring		

Gastrointestinal Issues in CHARGE Syndrome

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 drooling and secretion can be a problem; often due to poor swallowing.
- Mouth over stuffing and pocketing is prevalent.



Print outs available from website: www.drkimblake.com

Hudson #131/2015/619/05

Gastroesophageal Reflux (GER) and tube feeding



- Gastroesophageal Reflux is often severe and difficult to treat.
- Tube feeding is highly prevalent and maybe necessary for many years.
- Tube feed vs. Oral feeders have more:
 - Stomach pain
 - Discomfort when eating
 - Food and drink limits
 - Trouble swallowing
 - Nausea and vomiting
 - Constipation

Macdonald et al 2016 AJMG

"Motility issues" are a key problem.

Treatments for Gastroesophageal reflux

Behavioral

- Small meal sizes
- Decreased foods that increase GERD
- Elevation to 45 degrees after feeding
- Movement and keeping the body in an up right position.

Drugs

- Proton pump inhibitor – Nexium, prevacid.
- Motility agent's metoclopramide, cisapride
- Probiotics
- Treatments for constipation



Abdominal Pain

"The gut is different in CHARGE syndrome because of motility and microbiome abnormalities"

- Prevalent and difficult to evaluate with the underlining diagnosis often being missed.
- Digestion issues are clinically present. However there has been little research in this area.
- Anatomical structural issues such as "late volvulus" can occur.
- The brain gut feed back loop is affected



Straton, Hartshorne 2012 CHARGE non-verbal pain assessment (CNVPA)

Causes and Treatments for bloating and gas



Behavioral

- Exercise
- Massage
- Physiotherapy/Occupational/Rehab therapy

Diet

- FODMAPP
- Small meals less carbohydrate rich

Drugs/Supplements

- Prebiotics, probiotics
- Digestive enzymes, dandelion, ginger and fennel.
- Align (Probiotics)
- Chamomile

Constipation

This is a huge issue and gets lost in the many medical issues of CHARGE syndrome.

Possible Causes

- Abnormal or dysregulated innervation to the gut by the vagal nerve
- Gut dysmotility
- Anatomical abnormalities
- Behavioural or feeding issues
- Gut dysbiosis



CHARGE Constipation Video - Dr Kim Blake

Constipation Pamphlet

Constipation in CHARGE Syndrome
A Pamphlet For Families & Medical Professionals

Constipation
Constipation is an extremely common issue in CHARGE syndrome. It causes frequent bloating or visible bowel movement (i.e. it is visible) and a high incidence of regurgitation, which are signs of the acute gastroenteric tract dysregulation in CHARGE syndrome. There is evidence to link it to altered afferent, efferent, and/or vagal innervation.

Symptoms of Constipation

- Less than 3 bowel movements per week
- Dry, hard or lumpy stools
- Blood or is difficult or painful to pass
- Abdominal swelling or bloating
- Reduced appetite

Possible Causes

- Abnormal or dysregulated innervation to the gut by the vagal nerve
- Gut dysmotility
- Anatomical abnormalities
- Behavioural or feeding issues
- Gut dysbiosis

The Vagal Nerve
The vagus nerve (CN X) travels from the brain stem to the rest of the body. It is responsible for the regulation of digestion, heart and respiratory rate, as well as immune responses.

Abnormalities have shown abnormal gut motility in a small study of CHARGE syndrome.

Individuals with CHARGE syndrome have been shown to have and regulate the innervation to the gut, including abnormal peristalsis, dysregulation of contraction and relaxing emptying.

Prevention of Constipation

A general approach to constipation is often an 8-fold or so-fold increase in the quantity that comes along with constipation. This is that all normal individual's normal stools.

Medical interventions or strategies include:

- Adequate fluids
- Regular exercise
- Increased energy
- Diet
- Abdominal massage

Constipation Pamphlet

Proposed Role for the Vagal Nerve in Constipation

Abnormal vagal nerve innervation

Altered gut motility in the large bowel

Delayed or abnormal bowel emptying

Home of the microbiome

Rectum

References

Connections between the parasympathetic and sympathetic nervous systems are complex. The vagus nerve (CN X) is the longest cranial nerve in the body and is the primary motor and sensory nerve of the gastrointestinal tract. It is the primary motor and sensory nerve of the gastrointestinal tract. It is the primary motor and sensory nerve of the gastrointestinal tract.

Treatment of Constipation

Prevention includes:

- Adequate hydration
- Regular exercise
- Fiber-rich diet
- Avoidance of constipating medications
- Avoidance of constipating foods
- Avoidance of constipating beverages
- Avoidance of constipating supplements
- Avoidance of constipating herbs
- Avoidance of constipating vitamins
- Avoidance of constipating minerals
- Avoidance of constipating hormones
- Avoidance of constipating neurotransmitters
- Avoidance of constipating hormones
- Avoidance of constipating neurotransmitters

Behavioral interventions include:

- Scheduled toilet sitting
- Bowel training
- Massage
- Reflexology
- Herbal tea
- Acupuncture
- Yoga
- Tai Chi
- Pilates
- Tai Chi
- Pilates
- Tai Chi
- Pilates

Bowel Cleanout

Before treatment, consider the following:

- Hydration
- Fiber
- Exercise
- Avoidance of constipating medications
- Avoidance of constipating foods
- Avoidance of constipating beverages
- Avoidance of constipating supplements
- Avoidance of constipating herbs
- Avoidance of constipating vitamins
- Avoidance of constipating minerals
- Avoidance of constipating hormones
- Avoidance of constipating neurotransmitters

For more information:

www.charge.org

The role of the Vagal nerve (CNX)in constipation

Proposed Role for the Vagal Nerve in Constipation

Abnormal vagal nerve innervation

Altered gut motility in the large bowel

Delayed or abnormal bowel emptying

Home of the microbiome

Rectum

“The wandering nerve”

The vagal nerve is the longest cranial nerve in the body with sensory and motor fibers

Constipation - Treatments

Prevention:

- Fluids
- Exercise
- Behavioral therapy
- Diet
- Massage

Treatment:

- Polyethylene glycol PEG
- MiraLAX/Restoralax
- Senocot for motility issues
- Behavioral techniques/massage

Constipation and other GI issues in CHARGE Syndrome

Prevalence and quality of life

1. New study in 2023/2024 – Contact

- Dr. Kim Blake – k.blake@dal.ca
- Annie Kakamoussi – an834104@dal.ca

2. Sign up now and complete with Dr. Blake at the conference all individuals welcome, **you do not have to have GI issues**. It is a 20-minute online survey or in person.

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**

The diagram illustrates the gut microbiome's location and influencing factors. It shows a central 'Gut Microbiome' area with arrows pointing to 'Mouth', 'Stomach', and 'Intestines'. Surrounding this are icons for 'Diet', 'Stress', 'Genetics', and 'Antibiotics'.

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...

Gut microbiome pilot study of patients with CHARGE Syndrome and sibling controls.

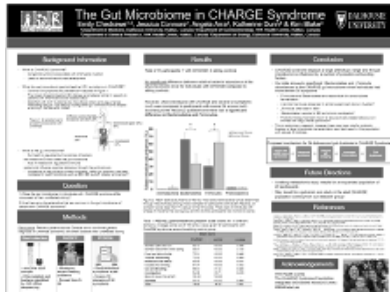
Emily Chedrawe, Jessica Connors, Angela Arra, Katherine Dunn, Kim Blake, Johana Van Limbergen

- 11 participants (CHARGE Syndrom = 7 sibling controls = 4)
- PASSFP + PEDSQL were used as standardized GI questionnaires
- Quality of life
-
-

The first photo shows a group of people standing in front of a banner for the CHARGE Syndrome Foundation. The second photo shows a group of people sitting at a table, possibly during a study session or meeting.

Funding by the IWK and the CHARGE syndrome foundation

The Gut microbiome in CHARGE syndrome

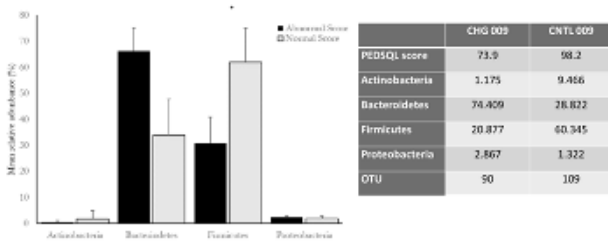


Results; PEDSQL gastrointestinal symptom scale score for 10 different domains (lower mean scores equal more severe symptoms)

	Mean Score		Standard Deviation		p-value
	CHARGE	control	CHARGE	control	
Stomach pain and hurt	82.14	100.00	24.26	0.00	0.099
Stomach discomfort when eating	88.57	100.00	17.49	0.00	0.135
Food and drink limits	73.81	100.00	26.86	0.00	0.042
Trouble Swallowing	72.62	100.00	19.07	0.00	0.009
Heartburn and Reflux	83.93	100.00	12.94	0.00	0.017
Nausea and Vomiting	91.07	100.00	11.33	0.00	0.082
Gas and Bloating	66.84	97.32	26.78	5.36	0.023
Constipation	54.08	85.71	24.87	6.52	0.015
Blood in bowel movement	100.00	100.00	0.00	0.00	-
Diarrhea	80.10	100.00	12.00	0.00	0.005

Results

Mean relative abundance of the four most abundant bacterial phyla determined through 16S DNA sequencing of stool samples for participants with severe PEDSQL GI symptom score (less than 77) (n=3) versus normal GI scores (n=8). Values found in Table 3.



Conclusion for Microbiome study



Gut microbiome poster

- The CHARGE microbiome is different
- 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



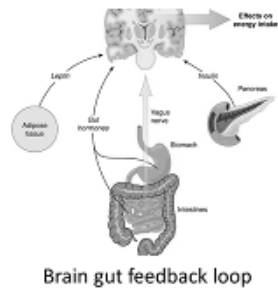
Conclusion

Individuals with CHARGE Syndrome with more severe GI issues have differences in their gut microbiome that are similar to those in Ehlers Danlos Syndrome (EDS), Autism Spectrum Disorder (ASD) and chronic constipation and irritable bowel syndrome.

	Bacteroidetes	Firmicutes	Protozoa
CHARGE Syndrome	↑	↓	↑
Autism Spectrum Disorder (de Angelis et al, 2015)	↑	↓	Not studied
Inflammatory Bowel Disease (Wu & Lewis, 2013; Dunn et al, 2016; Walters et al, 2014; Gophna et al, 2006)	↑	↓	↑

Up to date research references on gut microbiome

- Durack, J et al; (2019). The gut microbiome: Relationships with disease and opportunities for therapy. In *Journal of Experimental Medicine*. Rockefeller University Press.
- Gurram B, et al; Fecal microbiota transplantation in children: current concepts. *Curr Opin Pediatr*.(2019)
- Ho, L, et al; (2020). Gut microbiota changes in children with autism spectrum disorder: a systematic review. *Gut Pathogens*.
- Iglesias-vázquez, L., et al; (2020). Composition of gut microbiota in children with autism spectrum disorder: A systematic review and meta-analysis. In *Nutrients*
- Saurman, V., et al; (2020). Autism Spectrum Disorder as a Brain-Gut-Microbiome Axis Disorder. In *Digestive Diseases and Sciences* Springer.
- Vriesman MH, et al; Management of functional constipation in children and adults. *Nat Rev Gastroenterol Hepatol*. (2020)



GI Conditions that are missed and need to be on the differential diagnosis

- Abdominal migraine
- Pocketing/ Overstuffing of the mouth
- Cyclical vomiting
- Late onset Volvulus
- Dumping syndrome



Figure 10-3. A swallow prompt card

Sarah using the swallow prompt on the ipad

Abdominal migraine pamphlet

Raising Awareness of Abdominal Migraine in CHARGE Syndrome

A Pamphlet For Families & Medical Professionals

CHARGE Syndrome
A PARENTS' GUIDE TO THE SYNDROME
www.drinkimlake.com

Abdominal Migraine

Abdominal Migraine often occurs episodically, leaving severe, incapacitating, unpredictable and unresponsive symptoms.

Physicians need investigate for AM in patients with CHARGE Syndrome and other associated conditions.

Symptoms in CHARGE Syndrome

- Dull, aching, unilateral
- Location of symptoms
- Nausea and vomiting
- Pale, clammy, cool skin
- Light, noise, temperature sensitivity
- Behavior changes especially for nonverbal individuals

Risks to Misdiagnosis

- Perception of normal illness leading to inappropriate drug treatment
- Poor health outcomes
- Hospital admission

Triggers include

- Stress
- Poor sleep
- Missing a meal
- Travel, routine activities

Making a Diagnosis

- 7 days to 1 week of symptoms
- Abdominal pain does not always get necessary
- No family history

Prevention & Treatment

- Prognostic therapy
- Disruption of sleep, avoid caffeine, regular meals, improvement of constipation
- Managing anxiety and stress
- Medication for headache and vomiting
- Abdominal massage to relieve pain
- Bland diet

Print out available from website: www.drinkimlake.com

Abdominal migraine pamphlet

The Vagal Nerve

The vagus nerve (CN10) extends from the brain stem to the internal organs. It is responsible for the regulation of digestion, heart and respiratory rate, as well as reproductive activities.

Defect of this nerve have often abdominal gut motility in disorder in models of CHARGE Syndrome.

Specific work of vagus nerve from enteric and vagal nerve from vagus in the gut, resulting in abnormal peristalsis, dysregulate gut contraction and delay in emptying.

Gut Dysbiosis

An excess of decreased microbial diversity, that results in the overgrowth of pathogenic gut microorganisms.

Treatment that increase gut motility may improve the gut microflora.

See further evidence on gut motility on CHARGE Syndrome website.

Vagal & Enteric Nerve Dysfunction

Triggers:

- Stress
- Poor Sleep
- Missing a Meal

References:

Gomez, K., et al. Etiology and functional validation of glutamate receptor dysfunction in a genetic model of CHARGE Syndrome. PNAS 2016, 113(12):3281-3286.

Wang, Y. et al. Dysfunction of the vagus nerve in a genetic model of CHARGE Syndrome. PNAS 2016, 113(12):3287-3292.

More information on gut motility on CHARGE Syndrome website.

CHARGE CHARGE

CHARGE Syndrome

www.drinkimlake.com

Take home messages regarding Abdominal migraine

- More common if there is a family history of regular migraines
- Triggers – Stress, weather changes, dehydration and missing meals, poor sleep, travel.

Prevention

- Hydration therapy
- Lifestyle changes (Sleep hygiene, regular meals, prevention of constipation)
- Managing anxiety and stress

Treatment

- Improving gut microbiome (will be explored in further pamphlet)
- Abdominal massage to relieve pain
- NSAIDs

Late Volvulus in CHARGE Syndrome

Young man's story

- Chronic abdominal pain
- Thought to be secondary to poor gut motility and constipation
- Presented to ED with 2 days of vomiting with bile present in vomit; breath smelled of feces
- CT showed volvulus
- Surgery to manually rotate
- Pain resolved post-operatively
- There has been x2 recurrences which settled conservatively

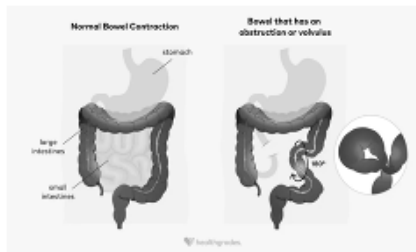
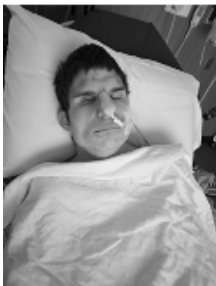


Image retrieved from <https://www.healthgrades.com/condition/abdominal-volvulus> May 24, 2023

Surgery recovery



Bowel Obstruction and Severe Constipation

Individual's Story

- Feeding and dysmotility issues since birth
- First bowel obstruction at age 15
- Over lifetime: multiple tests, CTs, surgeries to correct recurrent obstructions
- Multiple medications, prokinetics, prebiotics, and stool softeners
- Negative impact on quality of life, unable to leave house to attend work
- Bowel rest and possibly the use of a bowel stimulator in the future

Complex Gastrointestinal (GI) Issues in CHARGE Syndrome

Background

- CHARGE syndrome is a complex genetic condition characterized by multiple malformations, including eye, ear, facial, and skeletal anomalies.
- GI issues are common in CHARGE syndrome, often leading to severe constipation, reflux, and malabsorption.
- These symptoms significantly impact the individual's quality of life and may require surgical intervention.

Prevalence of GI Issues in CHARGE Syndrome

GI Issue	Prevalence in CHARGE Syndrome (%)	Prevalence in General Population (%)
Constipation	~80	~10
Reflux	~70	~15
Malabsorption	~60	~5
Intestinal Obstruction	~50	~2
Diarrhea	~40	~8
Other GI Issues	~30	~3

Diagnosis and Management

- GI issues in CHARGE syndrome are often diagnosed through a combination of clinical history, physical examination, and imaging studies (e.g., CT scans, MRI).
- Management is typically multidisciplinary, involving gastroenterologists, surgeons, and other specialists.
- Treatment options include dietary modifications, medications, and surgical interventions.

Conclusion

- GI issues in CHARGE syndrome are complex and require a multidisciplinary approach for diagnosis and management.
- Early identification and intervention are crucial for improving the individual's quality of life.

Cyclical Vomiting

Individual's story

- Young girl experienced vomiting for 3-6 days at a time
- Abdominal pain in morning, unrelieved, then vomiting would start
- Family history of migraines
- Started keeping a diary and noting any event that preceded an episode of vomiting
- Triggers identified: sleep dysregulation, stress, additives in food
- Management: modified diet, managing triggers, L-carnitine, Q-10
- Symptoms improved

Late Dumping Syndrome

- 17-year-old youth with CHARGE syndrome
- Reported feeling lightheaded, dizziness, blurred vision with dark spots about an hour after eating
- Classic signs of late dumping syndrome
- Caused by rapid emptying of stomach
- Common in people who have had gastric surgeries
- Treatment: modification to how and what you eat



Letter to the Editor | Free Access

Late Dumping Syndrome in a 17-Year-Old Female With Charge Syndrome

Mr Angeloslogos, Mr Alexandri-Hadziou, Professor Angela Kaya-Rizak, Dr Kim Blake

First published: 24 December 2017 | <https://doi.org/10.1111/jpc.13324>

Conflicts of interest: none declared.

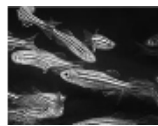
Etiology and functional validation of Gastrointestinal motility dysfunction in a zebra fish model of CHARGE syndrome

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 prokinetic agents.

Future:

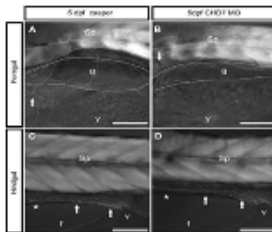
Zebrafish are an excellent model for studying compounds that improve GI motility in individuals with CHARGE syndrome.



Print out available from website: www.drkimblake.com

Clooney et al FEBS 285,11, 2018

Innervation of the CHARGE Zebrafish (chd7) and normal controls in the gut

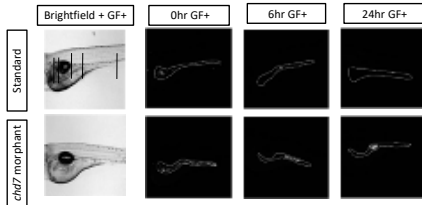


- Decreased enteric nerve branches around the fore gut (Compare A & B)
- Difference in size and shape of the gut in the CHARGE fish.

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

Clooney et al FEBS 285,11, 2018

Decreased motility shown in CHARGE zebrafish by delayed emptying of GI tract



*Florescent green = tagged food travel. GI tract of zebra fish over time



Knowledge Translation

International Collaboration is a key to success in a rare condition

- www.drkimblake.com A repository of Dr. Blake's research
- CHARGE Syndrome textbook, 2nd Edition
- International Education: MOOC (Massive Open Online Courses) via CHARGE Australasia Foundation-FREE- open to providers, learners, patients and families
<https://www.chargesyndrome.org.au/onlinecourse>



Questions and Answers



Thank you! From My family to your family
