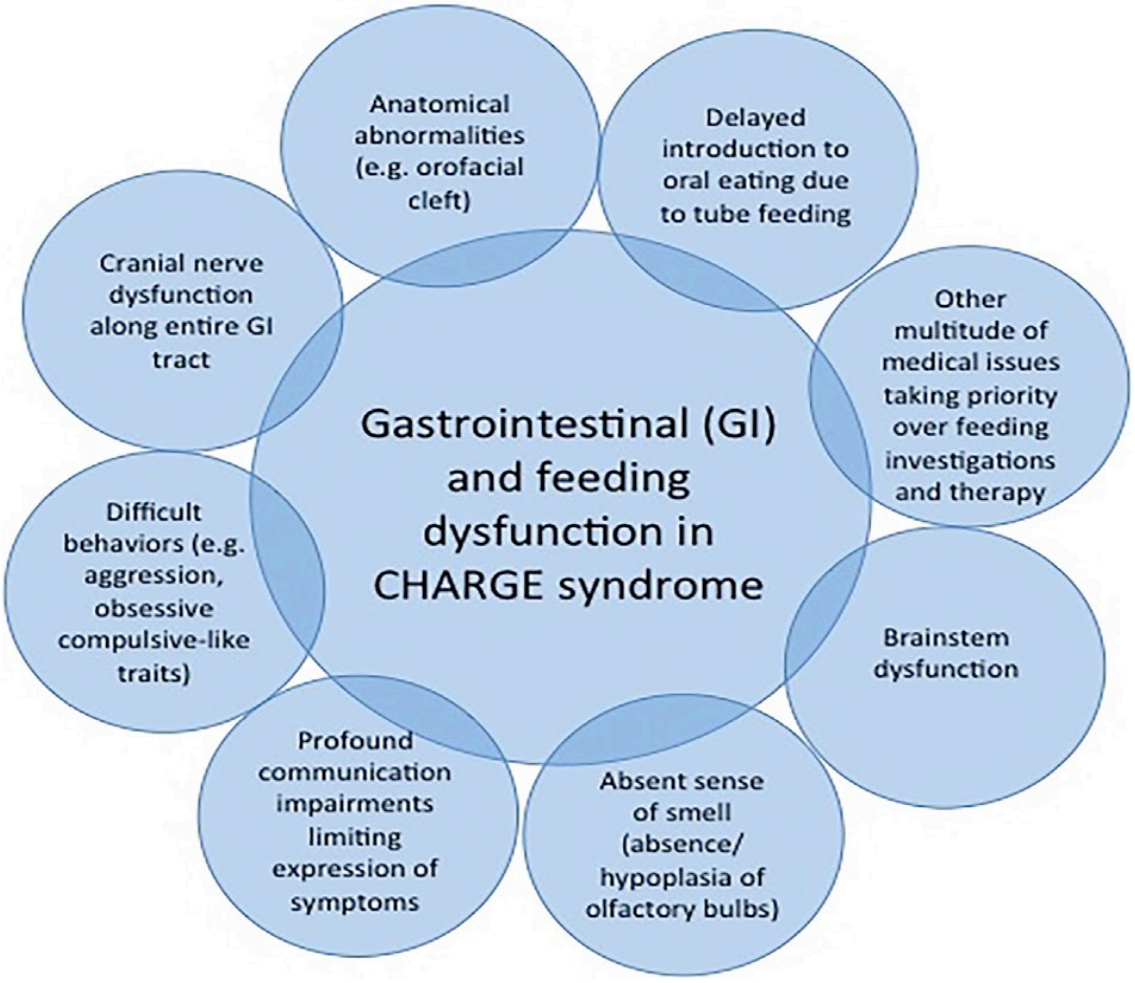
Gastrointestinal (GI) and feeding difficulties in CHARGE syndrome; the guts of it.

Dr. Kim Blake Professor, Dalhousie University
Pediatrician IWK Health Centre
14th International CHARGE syndrome conference – Professional Day

Introduction

The aim of this presentation is to discuss the gastrointestinal (GI) symptoms and feeding difficulties in CHARGE syndrome. Much of this presentation is based on the review paper titled "Gastrointestinal and feeding difficulties in CHARGE syndrome: A review from head-to-toe", authors Kim D. Blake, Alexandra S. Hudson American Journal Medical Genetics 2017; 1-11. This review paper is a useful resource for professionals and parents who want an overview of the GI issues in CHARGE syndrome.

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.



A visual lay out of the gastrointestinal (GI) feeding dysfunction in CHARGE syndrome.

The majority of clinical features seen in CHARGE syndrome contribute to the highly prevalent gastrointestinal (GI) and feeding difficulties; nearly 100% of individuals will experience feeding and/or GI dysfunction at some point in his/her lifetime. While almost 90% of individuals require nasogastric, gastrostomy or jejunostomy feeding tubes.

Morbidity/Mortality
GI symptoms contribute to extended hospitalizations, numerous diagnostic procedures and multiple trials of prescription medications. Initially thought to be more prevalent in infancy and childhood, researchers have highlighted the development of new feeding and GI issues that arise in adolescent and adulthood making GI issues one of the most pervasive and under estimated problems for individuals with CHARGE syndrome.

Anatomy
Individuals with CHARGE syndrome often have maxillary facial anomalies as well as small oral cavities and large tonsils which lead to a crowded oral cavity. This can result in problems such as drooling, sleep apnea and feeding issues. Tonsillectomy and adenoidectomy may help improve problems. Implantation of a hypoglossal nerve stimulator has been used in patients with Down syndrome but has not been described in CHARGE syndrome.

Salivation
Excessive salivation is linked to saliva dysphagia as a result of abnormal cranial nerve innovation (glossopharyngeal nerve). Excessive salivation can cause obstruction of the airways particularly in postoperative airway events. It is important that multiple procedures be combined under one anesthetic whenever possible. Botulinum toxic A (Botox) injection into the salivary glands can be effective in some individuals.

Aspiration and tube feeding
Aspiration is a major reason for exclusive tube feeding; it can result in recurrent pneumonias and is a major cause of mortality. Many individuals are dependent upon tube feeds in early life; sometimes continuing into later life. Individuals with CHARGE syndrome learn to swallow and use their tongue and oral oropharynx differently. They may not pass a feeding test but are able to tolerate certain textures orally.

Packing and mouth over-stuffing
This is often unrecognized and occurs most often with bread and pasta type foods. It can prolong meal times and result in leftover food in cheeks hours after the meal which can be a problem for dentition. Many individuals need to learn how to chew, swallow and control their tongue movements.

Choking
This is a worry for parents and often requires close supervision at meal times. Restriction of certain foods and textures may be necessary. Vascular rings should be considered and investigated for.

Cranial nerve dysfunction – Trigeminal nerve (CNV)

The trigeminal nerve (CN V) innovates the muscles of mastication and is responsible for sensation of the face. Abnormal function of this nerve can lead to dysfunctional chewing, risk of aspiration, pocketing, dysmotility and abnormal gag reflexes. Individuals often relearn how to coordinate chewing and swallowing.

Gastrointestinal reflux

This is very common and treatment is difficult. Many individuals undergo surgery called the Nissen fundoplication; however, there is a high rate of failure with medical management being the main stay of treatment. Anatomical variation is important to look for. This can take the form of small stomachs, dysmotility and abnormal gastric emptying.

Abdominal pain, bloating and late dumping syndrome

Pain can be very difficult to assess in individuals with CHARGE syndrome; the CHARGE non-vocal Pain Assessment Scale can be helpful to mitigate this unknown (Stratton & Hartshorne, 2016). A change in diet may be useful such as the FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet. Probiotics and massage have been used by parents.

Late dumping syndrome occurs about 1-3 hours after a meal resulting in perspiration, palpitations, hunger, weakness, confusion, tremor and syncope. Modifying diet (decreasing simple carbohydrates such as sweets and white bread) can be tried to relieve symptoms.

Bone health

Bone mineral density (BMD) can be decreased in CHARGE syndrome. This is the result of multiple factors including poor nutrition, decreased in weight bearing activities and low levels of sex hormones. Increasing intake of vitamin D (1,000 – 3,000 international units daily) weight bearing activities and hormone replacement is important to prevent decrease in bone mineral density.

Constipation

This is an issue that is often not addressed until it becomes a problem and the causes are multifactorial. These include abnormal innervation of the vagus nerve suppling the GI tract. Gastrostomy and jejunostomy tube feeding diet as well as maladaptive behaviors around toileting play an essential role.

Enteric nervous system dysfunction

The GI system in a zebrafish model of CHARGE syndrome shows a decrease in the numbers of enteric nerve branches and decrease motility, with delayed emptying of the GI tract (Cloney et al., 2016). This is yet to be studied in humans; however, biopsies of the lower GI tract in individuals with CHARGE syndrome have started to be performed and show abnormalities.

Future research

1. The Zebra fish model demonstrating GI motility in CHARGE syndrome is robust and has been successfully replicated in autism spectrum disorder. This model has the potential to use different drugs and combinations in order to evaluate gut motility. This will produce ideas for further clinical research.
2. Further studies should continue to analyze the entric nervous system and motility of the GI tract in individuals with CHARGE syndrome. This may require biopsies and functional studies.
3. The microbiome is being studied in a number of conditions and should produce useful data when studied in CHARGE syndrome.

Summary

The GI system should not be missed in CHARGE syndrome. We suggest physicians, therapists and parents use the CHARGE syndrome checklist by Trider et al., 2017 (appendix 1) and the feeding assessment scale (appendix 2) with all visits.
A multidisciplinary team approach is recommended including ENT, speech language pathology, feeding therapy and GI team.

Cranial and entric nerve dysfunction is the most promising area of future research and treatment options for feeding and GI dysfunction in CHARGE syndrome.

CHARGE SYNDROME CHECKLIST: HEALTH SUPERVISION ACROSS THE LIFESPAN (FROM HEAD TO TOE)

		INFANCY (0:2 years)	CHILDHOOD (3:11 years)	ADOLESCENCE (12:17 years)	ADULTHOOD (18+ years)
GENETICS	Clinical diagnosis (Blake et al. or Verloes or Hale et al. criteria)				
	Genetic testing – Genetics consult (CHD7 analysis, array CGH)				
	Genetic counselling				
NEUROLOGY	CNS malformations/hypoplasia olfactory bulb/temporal bone (semicircular canal) malformations – requires MRI/CT				
	Seizures – more common at older ages – consider EEG				
	Cranial nerve problems – monitor for absent sense of smell, facial nerve palsy, sensorineural hearing loss, vertigo, swallowing problems				
EYES, EARS, NOSE AND THROAT	Coloboma, risk of retinal detachment E Ophthalmology consult (dilated eye exam in infancy, vision assessments)				
	Corneal exposure – lubricating eye drops				
	Photophobia – tinted glasses, sunhat				
	Choanal atresia/cleft palate/tracheoesophageal fistula E ENT/Plastics consult				
	Audiometry and tympanometry, monitor for recurrent ear infections				
	Adaptive services for individuals with deafness/blindness				
	Cochlear implant assessment if applicable				
	Obstructive sleep apnea – monitor for tonsil/adenoid hypertrophy				
	Excessive secretions – consider Botox, medication				
	Dental issues – consider cleaning under anaesthetic				
CARDIOLOGY RESPIROLOGY	Cardiac malformations common – major/minor defects, vascular ring or arrhythmias possible (echocardiogram, chest x-ray, ECG) E Cardiology consult				
	Sinusitis, pneumonia, asthma E monitor				
	Anesthesia risk (difficult intubations/postop airway obstruction/aspiration) – extensive preoperative assessment, combine surgical procedures				
GASTROENTEROLOGY GENITOURINARY	Gastroesophageal reflux – Gastroenterology consult – consider motility agents with proton pump inhibitor				
	Poor suck/chew/swallow E feeding team assessment/intervention				
	Aspiration risk, tracheoesophageal fistula – swallowing studies				
	May need supplemental feeds – frequently requires gastrostomy tube or Gastro-jejunostomy tube				
	Constipation – consider Senna glycoside with polyethylene glycol				
	Renal anomalies – abdominal u/s +/E VCUG, blood pressure monitoring				
ENDOCRINOLOGY	Hypogonadotropic hypogonadism – LH, FSH by 3 months				
	Genital hypoplasia (if undescended testes E consider orchidoplexy)				
	Delayed puberty – Endocrinology consult E gonadotropin levels, HRT				
	Osteoporosis – DEXA scan				
	Poor growth – Endocrinology consult – GH stimulation test, GH therapy				
	Obesity E monitor				
	Fertility and contraception E discuss				
IMMUNE SYSTEM	Note presence of thymus at open heart surgery				
	Routine immunizations/antibody titres to immunizations in adolescence				
	Recurrent infections – Immunology consult				
MSK	Scoliosis/kyphosis monitor				
	Mobility (affected by ataxia, hypotonia) E evaluate				
PSYCHOLOGY DEVELOPMENTAL	Assess gross and fine motor skills – Occupational Therapy, Physiotherapy				
	Communication, language, writing abilities – Speech Language Therapy				
	Consider deafblind consultant				
	Prepare for transitions to school, situations, places, systems				
	Psychoeducational assessment, Individualized Education Plan				
	Sleep disturbances – consider melatonin				
	Behavior management – self regulation, impulse control, anxiety, obsessions, compulsions, anger				
	Toileting skills E support				
	Life skills/adaptive behaviour/social skills/social play				
	Address sexuality				
	Family stress – offer supports and resources				
	Medical self-management – work on managing medications, understanding conditions, seeing healthcare provider independently				

CHARGE SYNDROME CHECKLIST: HEALTH SUPERVISION ACROSS THE LIFESPAN (FROM HEAD TO TOE)

Abbreviations Used in Checklist

CGH E Comparative genomic Hybridization
CNS E central nervous system
CT E computed tomography
DEXA scan E dual energy Xray Absorptiometry
EEG E electroencephalogram
ENT E ear, nose and throat
FSH E follicle stimulating hormone
GH E growth hormone
HRT E hormone replacement therapy
LH E luteinizing hormone
MRI E magnetic resonance imagine
MSK E musculoskeletal
U/S E ultrasound
VCUG E voiding cystourethogram

Resources

- The CHARGE Syndrome Foundation (http://chargesyndrome.org/aboutEcharge.asp)
- The CHARGE Informational Pack for Practitioners (SENSE UK) (https://www.sense.org.uk/content/chargeEinformationEpackpractitioners)
- Book E CHARGE Syndrome (Genetics and Communication Disorders), 1st ed. Hartshorne TS, Hefner M, Davenport S, Thelin J. 2011
- OMIM Entry #214800 CHARGE Syndrome (http://www.omim.org/entry/214800)
- CHARGE Syndrome International Conference
- CHARGE Syndrome Listserv
- CHARGE Syndrome Facebook Group

Perkins School for the Blind eElearning (http://www.perkinselearning.org/videos)

- Deafblind International (http://www.deafblindinternational.org/index.html)
- Open hands, open access: deafEblind intervener learning modules (http://modele.nationaldb.org)

Key General References

1. Blake K, Prasada C. 2006. CHARGE Syndrome. Orphanet J Rare Dis 1:34
2. Brown D. 2005. CHARGE Syndrome "behaviors":Challenges or adaptations? Am J Med Genet Part A 133A: 268E272
3. Hsu P, Ma A, Wilson M, Williams G, Curotta J, Munns CF, Mehr S. 2014. CHARGE syndrome: a review. J Pediatric Child Health 50:504E511

Date: _____

Name of Individual: _____

Age:_____ Gender (Circle one): Male Female Not Disclosed

Completed By (Circle one): Mother Father Feeding Therapist Nurse/Physician Other:_____

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

0%	25%	50%	75%	95%

Circle one number on the scale:		Never	A Little	Sometimes	A lot	Always
1	He/she will refuse food when eating orally.	0	1	2	3	4
2	He/she takes longer than 45 minutes to eat orally.	0	1	2	3	4
3	He/she takes less than 15 minutes to eat orally.	0	1	2	3	4
4	He/she needs **close supervision** when eating orally.	0	1	2	3	4
5	He/she needs **someone in the room** when eating orally.	0	1	2	3	4
6	He/she has problems cutting food when eating orally.	0	1	2	3	4
7	He/she has problems feeding him/herself when eating orally.	0	1	2	3	4
8	He/she chokes or coughs when eating orally.	0	1	2	3	4
9	He/she has **trouble** chewing food.	0	1	2	3	4
10	He/she has **trouble** swallowing food.	0	1	2	3	4
11	He/she has to be **told or reminded** to chew.	0	1	2	3	4
12	He/she has to be **told or reminded** to swallow.	0	1	2	3	4
13	He/she does not like to mix food textures when eating (e.g. mixing puree and solid food).	0	1	2	3	4
14	He/she accidentally loses food out of his/her mouth during eating.	0	1	2	3	4
15	He/she will over-stuff his/her mouth with food during eating.	0	1	2	3	4

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 lets 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/drink)	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 lumpy 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	1
31	Hard vegetables and fruit (e.g. raw apples)	0	1

Total Score (sum of all items)	**/100 total points**
Circle one:	**Feeding difficulties:** **Mild (0-25 points)** **Moderate (26-50 points)** **Severe (51-100 points)**

TABLE 1 CHARGE syndrome characteristics and resulting feeding and gastrointestinal manifestations

	Phenotypic consequence	**Frequency in the CHARGE syndrome population Bergman et al. (2011); Hale et al. (2016)**	**Feeding and gastrointestinal manifestations**
Coloboma of the iris, retina, choroid, or disc (unilateral or bilateral)	- Visual impairment	75–89%	- Interfere with feeding process - Poor hand-eye coordination when feeding
Choanal atresia/ stenosis (unilateral or bilateral)	-Interruption in breathing through the nasal passage	38–61%	- Disturbance and incoordination of respiration during sucking
Cranial nerve (CN) dysfunction			
CN I (olfactory)	- Absent or decreased sense of smell	86–100%	- Decreased interest in food - Reduced taste
CN V (trigeminal)	- Dysfunctional muscles of mastication - Decreased sensation of face	86–100%	- Abnormal chewing - Decreased sensation around mouth can cause food falling out of mouth
CN VII (facial)	- Facial palsy - Abnormal taste sensation to the anterior 2/3 of tongue - Abnormal opening of upper esophageal sphincter - Abnormal hyoid and laryngeal movement	86–100%	- Interference with chewing ability - Decreased taste - Inability to retain salivary secretions or food in mouth - Pocketing of food into cheek
CN IX (glossopharyngeal)	- Abnormal taste to posterior 1/3 of tongue - Abnormal sensation to palate, tongue, pharynx	86–100%	- Pocketing of food into cheek - Overstuffing of food into mouth
CN X (vagus)	- Abnormal sensation and motor function of pharynx, larynx, base of tongue -Abnormal gastrointestinal peristalsis	86–100%	- Gastroesophageal reflux, which can result in aversion of solid foods - Esophageal dysmotility - Abdominal bloating and constipation
CN XI (hypoglossal)	- Impaired tongue movement	86–100%	- Inability to form food bolus - Inability to clear food from cheeks or palate
Developmental delay		76–100%	- Interfere with ability to learn oral feeding skills and safe feeding practices
Cleft lip and palate	- Abnormal connection between oral and nasal cavity	30–48%	- Ineffective or inefficient sucking due to an inability to close off the nasal passage
Cardiovascular	- Conotruncal defects and other major anomalies - Atrioventricular septal defects Vascular ring	72–92%	- Compression of esophagus, preventing food bolus mobility - Complications in maintaining coordination of sucking, swallowing, and respiration due to fatigue
Tracheoesophageal fistula	-Abnormal connection between the esophagus and trachea	18–29%	- Excessive salivation at birth - Choking, coughing, vomiting, and cyanosis with feeding at birth -Stenosis of esophagus following repair, requiring esophageal dilatations
Behavioral phenotype	-Social withdrawal, goal-directed persistent behavior, repetitive motor mannerisms	100%	- Aversion of certain food textures - Interference with mealtime—for example, does not want food to touch each other, must finish entire plate -Over-stuffing and food pocketing

gastrointestinal and feeding difficulties,

Table 2. A summary of currently available treatment options for

Gastrointestinal/feeding dysfunction	Currently available treatment options
Absent/decreased sense of smell	-Use of strong tasting foods
Anatomical anomalies (choanal atresia/stenosis, cleft palate/lip, larynx/pharynx defects, vascular rings, etc.)	-Surgical repair
Overcrowded oral cavity	-Tonsilectomy and adenoidectomy
Excess salivation	-Botulinum toxin A (Botox) injection into salivary glands -Combining multiple surgeries at one time to minimize use of anesthetic and risk of postoperative airway events
Aspiration	-Tube feeding (nasogastric, gastrostomy, jejunostomy) -Texture limited diet (e.g., puree only) -Feeding therapy to improve oral feeding skills -Treatment of gastroesophageal reflux disease
Packing (pocketing food into cheeks) and mouth overstuffinga	-Avoidance of bread/pasta type foods Liquid chasers (e.g., water, puree) after taking bites of food -Cutting food into small pieces
Choking	-Checking cheeks for any leftover food -Using a timer to pace swallowing and eating during meal time -Close supervision during eating -Texture limited diets
Cranial nerve dysfunction (CN V, VII, VIII, IX, X, XI)	-Feeding therapy to re-learn feeding process if neurological function improves with age -Potential for nerve stimulation (further research is needed)
Gastroesophageal reflux	-Pharmacological treatment -Nissen fundoplication (high failure rate and may need multiple repairs)
Abdominal pain and bloating	-Abdominal massage -Pharmacological treatment -Low FODMAP diet -Avoiding fermented food products
Late dumping syndrome	-Consuming smaller amounts of food at a time -Reducing simple carbohydrates (e.g., white bread, junk food)
Impaired gut motility	-Pro-motility agents (further research is needed)
Poor bone health	-Vitamin-D and calcium rich foods -Vitamin-D and calcium supplements -Weight bearing activities -May need hormone replacement therapy
Obesity	-Minimizing excess calorie intake -Assessing for problematic feeding behaviors such as mouth over-stuffing -Increasing physical activity
Constipation	-Pharmacological treatment -Enemas
Feeding behaviors (e.g., repetitive behavior, anger at mealtime)	-Feeding therapy