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Mini Review

CHARGE syndrome gastrointestinal involvement: from mouth to anus

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CHARGE syndrome is an autosomal dominant disorder that occurs as a result of a heterozygous loss-of-function mutation in the chromodomain helicase DNA-binding (*CHD7*) gene, which is important for neural crest cell formation. Gastrointestinal (GI) symptoms and feeding difficulties are highly prevalent but are often a neglected area of diagnosis, treatment, and research. Cranial nerve dysfunction, craniofacial abnormalities, and other physical manifestations of this syndrome lead to gut dysmotility, sensory impairment, and oral–motor function abnormalities. Over 90% of children need tube feeding early in their life and many experience weak sucking/chewing, gastroesophageal reflux disease (GERD), and aspiration. The mainstay of treatment thus far has consisted of feeding therapy, GERD medications, Nissen fundoplication, gastrostomy/jejunostomy, and food texture limitation. Owing to the multitude of severe medical issues associated with this genetic disorder, GI involvement is often overlooked. Here, we report on five patients with CHARGE syndrome who manifested a range of severe GI and feeding difficulties.

Conflict of interest

None declared.

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Key words: CHARGE syndrome – cranial nerve dysfunction – feeding difficulties – gastrointestinal – gastroesophageal reflux disease (GERD) – abnormal motility

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CHARGE syndrome is a genetic disorder with an estimated incidence of 1 in 10,000–15,000 live births (1, 2). It was first described in 1979 as a pattern of nonrandom congenital anomalies including **C**oloboma of the eye, **H**eart defects, **A**tresia of the choanae, **R**etardation of growth and development, **G**enitourinary abnormalities, and **E**ar anomalies (CHARGE) (3, 4). Later on, more features were added to the clinical diagnostic criteria, including the highly prevalent cranial nerve dysfunction, and the four C's were coined: **c**ranial nerve dysfunction, **c**oloboma of the eye, **c**haracteristic ear abnormalities, and **c**hoanal atresia (5). The *CHD7* genetic mutation that is responsible for CHARGE syndrome was first discovered in 2004, and predominantly consists of heterozygous single nucleotide variants that affect protein function on the q12 arm of chromosome 8 (6). This loss-of-function mutation disrupts chromodomain helicase DNA-binding, which is essential for neural crest cell formation. CHARGE syndrome is inherited in an autosomal dominant pattern; however, many cases occur through sporadic *de novo* gene mutations (1). CHARGE syndrome remains a clinical diagnosis, which can be confirmed with genetic testing, and encompasses many physical features beyond the original CHARGE acronym (2, 7).

Gastrointestinal (GI) complaints are the most frequently reported symptoms in individuals with CHARGE syndrome (8, 9). These difficulties often begin at birth and can persist throughout the entire lifespan. Initially, anatomical malformations interfere with feeding and require surgical repair, including choanal atresia/stenosis, cleft palate/lip, and tracheoesophageal fistula (8–10). The most common GI complaints are gastroesophageal reflux disease (GERD), dysfunctional swallowing, excessive salivation, abnormal feeding behaviours (e.g. pocketing food into the cheeks), abdominal pain, and constipation (8, 9, 11). The GI issues are thought to be due largely to cranial nerve dysfunction and abnormal GI tract motility (12, 13). The mainstay of treatment options thus far consists of

Fig. 1. Two individuals with CHARGE syndrome using gastrostomy tube feeding.

medication management, Nissen fundoplication, gastrostomy/jejunostomy feeding tubes, feeding therapy with a speech language pathologist/occupational therapist, botox injections into salivary glands, and food texture limitations placed on the diet (e.g. puree food only). Over 90% of individuals also need some form of tube feeding (nasogastric, gastrostomy, or jejunostomy) for feeding difficulties or aspiration risk (8, 9) (Fig. 1). It has recently been proposed that the clinical diagnostic criteria for CHARGE syndrome should be expanded to now include swallowing and feeding difficulties as new diagnostic criteria, highlighting the high prevalence of GI involvement in this genetic disorder (14).

Objective

To describe five patients who illustrate the wide range of GI symptoms, from mouth to anus, in CHARGE syndrome across the lifespan (Tables 1 and 2). Informed consent was obtained from all patients and their parents for being included in the study.

Case 1

An 18-year-old female patient was diagnosed with CHARGE syndrome soon after she was born. Throughout her life, she needed close supervision during eating as she would eat excessively, over-stuff food into her mouth, and eat at a very rapid pace. She required mashed food only and was working with feeding therapists to take appropriate bite sizes and to reduce her speed of eating. She also suffered from insomnia, obstructive sleep apnea, and obsessive-compulsive behaviours. She was living in a residential home, in which she was supervised and observed closely during eating. During a lunchtime meal when she was not under close supervision, she was redirected to slow down her eating but started to choke and stopped breathing. First aid and cardiopulmonary resuscitation (CPR) were performed as she was transferred to the hospital. Attempts to intubate had failed and a tracheostomy was performed. At the hospital many interventions took place, including direct laryngoscopy, esophagoscopy with foreign body removal, fiberoptic tracheobronchoscopy, and a revised tracheotomy. Broccoli and mashed vegetables were found in the esophageal lumen and a high tracheotomy was done. The patient was transferred to the critical care unit but her oxygen saturation remained low and she was returned to the operating room for a further revision of her tracheotomy. A fiberoptic scope examined the tracheobronchial tree and no foreign bodies were noted. She remained in critical condition at the end of the procedure with low oxygen saturation and blood pressure. Unfortunately, the patient died in the intensive care unit later that same evening, with the official cause of death identified as choking.

Case 2

A 15-year-old female patient was diagnosed with CHARGE syndrome at age 1 year. She had required gastrostomy tube feeding from age 1 to 8 years. She presented with increased saliva production and problematic feeding behaviours of pocketing food into her cheeks during mealtime. Saliva would constantly pool in her mouth and wet her lips and chin. The patient would not spontaneously swallow and would have to be constantly prompted by her caregivers. Food would rest on her tongue or in her cheeks without swallowing, which caused her to gag during eating approximately four times a week. Food would also be found in her cheeks hours after a meal had ended. Botox was injected into the submandibular and parotid salivary glands every 6 months to reduce saliva production. To reduce risk of choking, she was restricted to purees and minced foods. She worked with a speech language pathologist and began to use an electronic device that prompted her to swallow every 30 s, which greatly reduced her frequency of pocketing food into her cheeks, number of choking episodes, and pooling of saliva.

Case 3

An 8-year-old male had a confirmed genetic diagnosis of CHARGE syndrome. He required supplemental nasogastric tube feeding after birth and had a Nissen fundoplication with G-tube placement at age 10 months. He required a tracheostomy at 6 weeks of age for subglottic stenosis in addition to his severe laryngomalacia, with later repair of his cleft lip. From the age of 10 months he had not been able to feed orally and had difficulty swallowing secretions, resulting in drooling and 'spitting' requiring frequent suctioning despite regular Botox injections of the salivary glands. He had severe oral aversion in his early years and also intermittent constipation. He had suffered from repeated periods of enteral feed intolerance with symptoms of severe pain, bloating, as well as gagging, and vomiting. These symptoms had been resistant to maximal pharmacological management of his GERD, different regimes of continuous or intermittent G and GJ feeding, as well as different types of hypoallergenic formulas and blenderized feeds. Intolerance of enteral feeds was so extreme that

Table 1. Demographic and gastrointestinal data from five individuals with CHARGE syndrome

	Gender	Age (years)	Age at diagnosis (years)	Tube feeding duration (years)	GERD medication use	Nissen fundoplication procedure	Texture-limited diet
1	Female	18[a]	0	0	Yes	No	Yes
2	Female	15	1	8	Yes	No	Yes
3	Male	8	0	8	Yes	Yes	Yes
4	Female	11	0	11	Yes	Yes	Yes
5	Male	9	1.5	9	Yes	Yes	Yes

GERD, gastroesophageal reflux disease.
[a]Deceased.

Table 2. Major and minor phenotypic CHARGE syndrome features from five individuals with CHARGE syndrome

	Frequency in general CHARGE population (2)	Case 1	Case 2	Case 3	Case 4	Case 5
Major CHARGE characteristics						
Ear abnormalities[a]	90–100%	Yes	Yes	Yes	Yes	Yes
Abnormal semicircular canals		Yes	Not tested	Yes	Yes	Yes
Coloboma (retina/iris)	75–90%	Yes	Yes	Yes	Yes	Yes
Choanal stenosis/atresia	65%	Yes	Yes	Yes	Yes	Yes
Cranial nerve dysfunction	50–90%	Yes	Yes	Yes	Unknown	Unknown
CN I (difficulty smelling)		Unknown	Yes	Yes	–	–
CN VII (facial palsy)		No	Yes	Yes	–	–
CN VIII (difficulty hearing)		Yes	Yes	Yes	–	–
CN IX, X, XI (difficulty swallowing)		Yes	Yes	Yes	–	–
Minor CHARGE characteristics						
Developmental delay	>70%	Yes	Yes	Yes	Yes	Yes
Heart defect	50–85%	Yes	Yes	Yes	Yes	Yes
Cleft lip	15–20%	No	No	Yes	No	No
Cleft palate	15–20%	No	No	Submucous	No	No
Genital hypoplasia	50–70%	No	No	No	No	Yes
Growth deficiency	70–80%	Yes	Yes	No	Yes	Yes
Tracheoesophageal fistula	Unknown	No	No	No	No	No
Urinary tract problems	Unknown	Yes	No	No	Unknown	Unknown

[a]Ear abnormalities include external, middle, and inner ear abnormalities.

he spent a 6-month period on total parenteral nutrition (TPN) through a central line at home, with total bowel rest and only occasional minimal tube feeds. Intermittent bouts of extreme agitation and distress were felt to originate from the GI tract and were initially considered to be related to abdominal 'migraine'. These too have been resistant to many different types of pharmacotherapy and non-pharmacologic interventions. Investigations over the years through multiple hospital admissions included thorough laboratory testing, extensive imaging, as well as multiple endoscopic examinations of both the upper and lower part of the GI system. One of many imaging tests revealed a possible adhesion near the terminal ileum, which was released laparoscopically with some subjective improvement in pain but no improvement in enteral feed tolerance.

Case 4

An 11-year-old female patient received a clinical diagnosis of CHARGE syndrome within hours of birth. She had been exclusively tube fed since birth. At 7 weeks old, she underwent a Nissen fundoplication surgery for problematic GERD and aspiration. This procedure was unsuccessful and required multiple revisions that resulted in a hiatal hernia and severe abdominal adhesions. Since infancy, she had been suffering from abdominal migraines and cyclical vomiting. She had failed all medical therapies and experienced episodes of severe vomiting with tachycardia, diaphoresis, and mottled skin, which occurred every 2 to 3 weeks, lasting 3 days at a time. Relief was only found after 12 to 24 h of complete gut rest. In addition, she developed gastritis with linear stomach ulcers, which bled when venting her gastrostomy tube, as well as small bowel lymphoid hyperplasia. Other medical problems (e.g. ear infections) often first presented with GI symptomatology. As a result of these significant GI issues, adequate growth and nutrition have been difficult to achieve.

Case 5

A 9-year-old male patient received a gene-confirmed diagnosis of CHARGE syndrome at 18 months of age.

Table 3. An overview of the common gastrointestinal and feeding issues experienced in CHARGE syndrome, from mouth to anus (8, 9)

Common issues	Contributing factors
Abnormal sense of smell	• Cranial nerve dysfunction (CN I) • Choanal atresia/stenosis
Difficulty with textures (e.g. does not want to eat lumpy food)	• Difficulty integrating oral sensory information • Gastroesophgeal reflux • Prolonged orogastric or nasogastric tube feeding
Excessive salivation	• Poor swallowing
Food selectivity or refusal	• Negative feeding experiences with gagging, choking, coughing, aspiration • Behavioral issues (i.e. OCD, autistic-like, tactile-sensory issues) • Gastroesophageal reflux
Poor chewing	• Cranial nerve dysfunction (CNV, CNVII) interfering with muscles of mastication • Delayed introduction of oral feeding
Pocketing of food into cheeks (packing) and over-stuffing food into mouth	• Cranial nerve dysfunction (CNV) causing reduced sensory awareness • Poor chewing • Poor swallowing • Abnormal smell • Behavioral issues
Poor swallowing	• Congenital cardiovascular arch anomaly (vascular ring) compressing esophagus/trachea • Cranial nerve dysfunction (CN IX, X, XI) • Cleft palate • Laryngeal malformations (laryngomalacia, laryngeal clefts) • Esophageal deformities (esophageal atresia, tracheoesophageal fistula) • Delayed introduction of oral feeding • Enlarged adenoids and tonsils
Aspiration (acute and chronic)	• Cranial nerve dysfunction (CNX) • Poor swallowing • Excessive salivation
Gastroesophageal reflux disease (GERD)	• Dysmotility issues due to cranial nerve dysfunction (CNX) • Small stomach
Abdominal bloating, pain, discomfort	• Dysmotility issues due to cranial nerve dysfunction (CNX) • Abdominal migraine
Constipation	• Cranial nerve dysfunction (CNX) • Food selectivity or refusal • Behavioral issues (i.e. OCD, autistic-like, tactile-sensory issues)
Anxiety around eating	• Poor chewing/swallowing • Difficulties with food textures

CN, cranial nerve; OCD, obsessive compulsive disorder.

He had been exclusively tube fed since birth. He had undergone Nissen fundoplication surgery, which successfully controlled his GERD. Unfortunately a presumed consequence of the procedure was excessive gas and bloating. This caused frequent abdominal discomfort. Despite daily use of laxatives and increased fiber, bowel regulation remained a great challenge, alternating between constipation and diarrhea. This played a major role in his behaviour. When constipated, he engaged in aggressive and self-injurious behaviour that would only resolve with a bowel movement. Toilet training was difficult due to the fact that he would avoid having a bowel movement on the toilet by jumping around and withholding stool. This exacerbated his constipation and bowel dysregulation.

Discussion

The impact of GI dysfunction and feeding difficulties on individuals with CHARGE syndrome and their families is profound. This has been identified as a major cause of morbidity and mortality for individuals of all ages with this genetic disorder (15). One study investigating death in childhood in CHARGE syndrome found that those who died before age 10 years were significantly more likely to have GERD, feeding difficulties, and breathing difficulties than those who survived beyond age 10 (10). An overview of the common GI and feeding issues experienced in CHARGE syndrome is summarized in Table 3.

GI issues are often overlooked during early infancy, even when more than 90% of babies will need some form of tube feeding, with many requiring long-term gastrostomy or jejunostomy tubes (8, 9). GI and feeding issues remain a focus for the parents but again are not high on the list of priorities as the child ages and has to deal with a seemingly endless list of complex healthcare issues and medical specialist appointments. A recent study examined the health care utilization of five infants with CHARGE syndrome in Sweden, and found that in just 1 year they were hospitalized between 26 and 230 days, needed 10–34 diagnostic procedures, and were prescribed 10–28 different medications (16). Despite the extensive number of health issues these individuals face, the impact of GI symptomatology and feeding difficulties cannot be overstated.

The pathophysiology underlying the common GI and feeding problems in CHARGE syndrome is still not completely understood. CHARGE syndrome is mainly caused by a mutation in the *CHD7* gene, which codes a chromodomain helicase DNA binding protein (1). This causes a disruption in the chromatin remodeling and its important regulation of gene expression in embryogenesis. Cranial nerve dysfunction, a hallmark feature of CHARGE syndrome, is one of the most important factors in feeding difficulties in this genetic disorder (12). This is due to the cranial nerves' motor and sensory innervation of the anatomical regions essential for feeding: the head, neck, and GI tract. A recent study found that zebrafish models of CHARGE syndrome displayed reduced vagal innervation of the GI tract, decreased intestinal size, and impaired gut motility (13). This same study also found that prokinetic agents were able to improve the gut motility and rate of GI emptying in the CHARGE syndrome zebrafish models (13). This highlights the impact of cranial nerve dysfunction, with reduced organ innervation likely being one of the most important underlying pathophysiologic mechanisms of the GI and feeding problems experienced.

Feeding difficulties are most often present from day one of life, due to complex anatomical malformations including cardiovascular anomalies, cleft lip and palate, tracheaesophageal fistula, laryngeal malformations, choanal atresia and stenosis, and extensive cranial nerve dysfunction (1). Introduction of oral feeding is often delayed due to these anatomical abnormalities interfering with both oral motor skills and respiration (8). Enlarged adenoids and tonsils, which are common in CHARGE syndrome, can also compromise the pharynx and larynx, leading to swallowing difficulties (17). GI tract interventions have been found to be the second most common surgical procedure performed in CHARGE syndrome (18). Surgical correction of anatomical malformations and removal of enlarged adenoids and tonsils can also lead to improvement of feeding difficulties.

Serious feeding problems have also recently been linked to congenital arch vessel anomalies in CHARGE syndrome (19). An index patient was reported who had severe feeding problems that subsequently resolved following surgical repair of the aortic arch (19). Therefore, it is important to search for a congenital arch vessel anomaly. Surgical correction has the potential to improve feeding issues, particularly if there is compression of the esophagus or trachea.

Mouth over-stuffing and pocketing of food into cheeks, also known as packing, has been previously reported as a problematic feeding behaviour in children with autism, Down syndrome, and in those transitioning from tube to oral feeding (20–22). It has also recently been reported in CHARGE syndrome with parental worry regarding choking as a common reported consequence of the child overstuffing and packing food in their cheeks (11). This study also found that lumpy/mashed food was one of the most common textures of food to be overstuffed and packed, as was reported in the first patient in this review, who overstuffed, and consequently choked on, broccoli and mashed vegetables (11). These problematic feeding behaviours are thought to be due to cranial nerve dysfunction, resulting in hyposensitivity in the oral cavity, as well as abnormal motor coordination of the muscles of mastication and swallowing (11, 12, 23, 24). Feeding therapy with a speech language pathologist or occupational therapist early in the course of feeding difficulties may help reduce these adverse feeding behaviours.

Cranial nerve dysfunction is thought to contribute to weak sucking, weak chewing, swallowing difficulties, GERD, and chronic aspiration (12). One study found that 60% of children with CHARGE syndrome had aspiration when evaluated with video swallow study or flexible endoscopic evaluation (25). Sense of smell (cranial nerve I) is also impaired or absent in the majority of

individuals with CHARGE syndrome, which contributes to reduced taste and thus may result in overstuffing and packing feeding behaviours (11, 26). In addition, over 90% of children with CHARGE syndrome also have difficulties chewing and swallowing textured foods, which is thought to be in part due to oral tactile sensitivity from cranial nerve abnormalities (9).

Feeding difficulties, tube feedings, and sensory aversion to certain food textures can make it difficult to achieve a balanced diet that has the recommended amount of nutrients and vitamins. A previous study found that the recommended nutritional intake for calcium and vitamin D were not being met by 41% and 87%, respectively, of their CHARGE syndrome study population (27). Obesity has also been identified as a common problem occurring in the later years in CHARGE syndrome, therefore the addition of a dietician to the healthcare team of the individual is paramount.

Increased salivary secretions are a common problem, and can be difficult to manage. It has been reported that 80% of children with CHARGE syndrome had abnormal swallowing, which led to pooling of secretions in many cases (25). Botox injections into the submandibular and parotid salivary glands have been found to be successful in reducing the amount of secretions (28). This can help reduce aspiration and risk of choking on saliva. But as with the third patient in this review, botox injections may not always be the answer.

Reflux is one of the most common GI issues in CHARGE syndrome. Over 60% of adolescents and adults report ongoing reflux in a Canadian surveillance study, of which half required placement of a gastrostomy tube due to the severity of their reflux (15). Furthermore, a recent study in the UK found that reflux was the number one reason for prescription of medications in CHARGE patients (29). Nissen fundoplication procedure is often used to control severe GERD. Unfortunately, children with CHARGE syndrome are at increased risk for this procedure to fail (30, 31). Therefore, many individuals require ongoing pharmacological management and may need multiple fundoplication revisions.

Constipation is an under-recognized problem in children with a wide variety of genetic syndromes (31,32). This is also true in CHARGE syndrome, and often requires management with osmotic and stimulant laxatives and increased fiber. Constipation may also cause discomfort and pain in response to feeding, thereby exacerbating feeding behaviors and difficulties (33).

Behaviour of children with CHARGE syndrome has previously been described as involving autistic-like social withdrawal, repetitive behaviour, and repetitive motor mannerisms (34–36). This behaviour phenotype is thought to be mainly adaptive in response to the severe combined visual and hearing impairment, as well as related to problems with self-regulation. These behaviours can make bowel regulation very difficult to teach and sustain. Repetitive behaviours can also significantly interfere with daily routines as well as mealtime eating (9, 11). Anxiety around eating has also been identified in CHARGE syndrome, particularly as children grow into adulthood (11, 37, 38). Assessment of anxiety in regards to feeding issues by a psychologist, psychiatrist, and/or general pediatrician is an important part of the healthcare management of all individuals with this genetic disorder.

A validated scale specific for CHARGE syndrome feeding difficulties is currently being developed for use in both pediatric and adult populations. Current feeding and GI scales validated for the typically developing pediatric population such as the Pediatric Assessment Scale for Severe Feeding Problems (PASSFP©) and the PedsQL™ Gastrointestinal Symptoms Scales can also be used to assess and track the severity of these under recognized issues in CHARGE syndrome (39, 40).

A summary of the recommended investigations and management of the common GI and feeding difficulties experienced in CHARGE syndrome are listed in Table 4.

In the future, potential treatment options for the GI dysmotility issues that are highly prevalent in individuals with CHARGE syndrome should be explored. The focus

Table 4. Recommended investigations and management of common gastrointestinal and feeding difficulties in CHARGE syndrome

- Surgical repair of choanal atresia, cleft lip/palate, cardiac abnormalities, tracheoesophageal fistula
- Check for vascular ring
- Early involvement of a gastroenterologist (especially for GI dysmotility issues)
- Cranial nerve assessment by neurologist or ENT surgeon with associated radiological scans
- Investigate swallowing mechanism and gastroesophageal reflux
- Early feeding team assessment and ongoing therapy for feeding difficulties (speech language pathologist, occupational therapist, psychologist)
- Investigate for packing (pocketing of food in cheeks) while eating
- Potential use of nerve stimulation and nerve reconstruction for swallowing problems (new but unresearched therapy)
- Medication management for GERD (including motility agents/prokinetics)
- Consider Nissen fundoplication for GERD, but be cautious as failure rate and recurrent procedure rate is high
- Botox injections into salivary glands for excessive salivation
- Assessment of tonsils and adenoid enlargement by sleep studies and ENT surgeon
- Assessment of adequate vitamin D and calcium intake to protect bone development (i.e. by dietician)
- Medication management, osmotic/stimulant laxative use, and/or increased fiber for constipation
- Behavioral management of constipation (i.e. psychologist, deaf/blind specialist)
- Assessment of anxiety regarding feeding (i.e. psychologist, psychiatrist, general pediatrician) and potential treatment with anxiolytics
- Assessment of obesity in adolescence and later years
- Continued monitoring of new GI and feeding difficulties appearing in adolescence and adulthood

ENT, ear nose throat; GERD, gastroesophageal reflux disease; GI, gastrointestinal.

may need to move away from GERD treatment and instead towards motility agents. Future research should also compare GI problems in individuals with CHARGE syndrome to individuals with other genetic disorders and conditions with developmental delay such as autism. A feeding scale specific for CHARGE syndrome is currently being developed and validated and will be able to help in evaluating outcomes.

Conclusion

GI dysfunction, from mouth to anus, is a significant and pervasive clinical manifestation of CHARGE syndrome over the entire lifespan. Owing to the multitude of severe physical manifestations in this genetic disorder, GI involvement is often overlooked. The majority of individuals need some form of tube feeding during infancy, but feeding difficulties are often forgotten once the individual transitions to oral feeding and into adolescence and adulthood. Abdominal pain and bloating, GERD, constipation, swallowing difficulties, abdominal migraine, and problematic feeding behaviours are some of the most common GI complaints. It is important to identify and manage GI symptoms throughout the individuals' life in order to reduce the risk of the further health problems and death, and improve their quality of life. The associated morbidity and mortality cannot be overstated. Individuals with CHARGE syndrome need multidisciplinary feeding teams to be a part of the management of their care in order to address the broad spectrum of GI difficulties arising from medical, developmental, and behavioral issues – from infancy to adulthood.

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