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RESEARCH REVIEW

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Gastrointestinal and feeding difficulties in CHARGE syndrome: A review from head-to-toe

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CHARGE syndrome is an autosomal dominant genetic condition that is primarily diagnosed based on clinical features, with genetic testing available for confirmation. The CHARGE mnemonic stands for some of the common characteristics: coloboma, heart defects, atresia/stenosis of the choanae, retardation of growth/development, genitourinary anomalies, and ear abnormalities (CHARGE). However, many of the common clinical features are not captured by this mnemonic, including cranial nerve dysfunction, considered by some to be one of the major diagnostic criteria. Over 90% of individuals experience feeding and gastrointestinal dysfunction, which carries great morbidity and mortality. The aim of this review is to examine the nature of gastrointestinal (GI) symptoms and feeding difficulties in CHARGE syndrome, focusing on their underlying pathology, associated investigations, and available treatment options. We also provide information on available tools (for parents, clinicians, and researchers) that are important additions to the lifelong healthcare management of every individual with CHARGE syndrome. We review how cranial nerve dysfunction is one of the most important characteristics underlying the pervasive GI and feeding dysfunction, and discuss the need for future research on gut innervation and motility in this genetic disorder.

KEYWORDS
CHARGE syndrome, cranial nerve dysfunction, feeding difficulties, gastrointestinal dysfunction, gut motility

1 | INTRODUCTION

CHARGE syndrome is an autosomal dominant genetic condition, occurring approximately one in 10,000 to 15,000 live births. Although the diagnosis of CHARGE syndrome can be confirmed with genetic testing, it remains primarily a clinical diagnosis using Blake et al. (1998) and Verloes (2005) criteria. While genetic testing (gene *CHD7* analysis) can help the diagnosis, the phenotype cannot be predicted from the genotype (Bergman et al., 2011). The clinical features are variable and exist on a broad spectrum in terms of severity (Davenport, Hefner, & Mitchell, 1986). The term "CHARGE syndrome" was first coined by Hall (1979) and Hittner et al. (1979) to describe a constellation of signs and symptoms: Coloboma of the eye, Heart abnormalities, Atresia/stenosis of choanae, Retardation of growth and development, Genitourinary anomalies, and Ear abnormalities. However, some of the most common clinical manifestations of the syndrome (major and minor diagnostic criteria) are not captured by this term, including cranial nerve manifestations, semicircular canal abnormalities, cleft lip/palate, among many others (Blake & Prasad, 2006; Hale, Niederriter, Green, & Martin, 2016; Hsu et al., 2014; van Ravenswaaij-Arts, Blake, Hoefsloot, & Verloes, 2015). The majority of the clinical features seen in CHARGE syndrome, both alone and in combination with each other, contribute to the highly prevalent gastrointestinal (GI) and feeding difficulties (Figure 1) (Hudson, Trider, & Blake, 2017; Hudson, Macdonald, Friedman, & Blake, 2017). Nearly 100% of individuals will experience feeding or GI dysfunction at some point in his/her life,

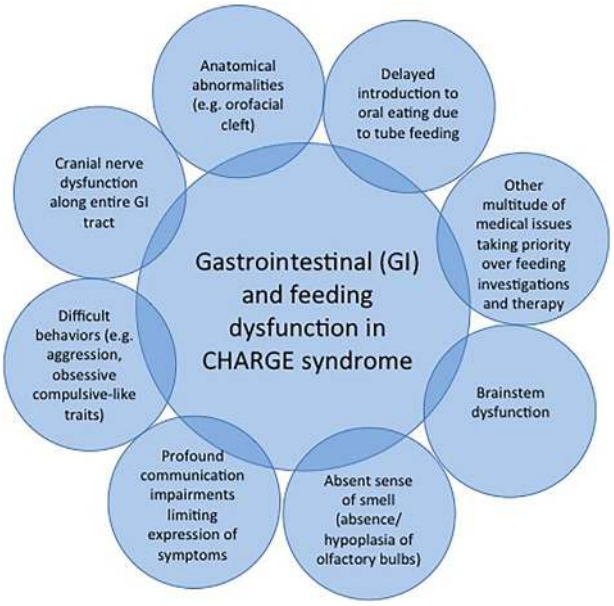

FIGURE 1 A highlight of the multitude of factors contributing to gastrointestinal and feeding dysfunction in CHARGE syndrome

including over 90% needing nasogastric, gastrostomy, or jejunostomy tube feeding (Figure 2) (Blake, Russell-Eggitt, Morgan, Ratcliffe, & Wyse, 1990; Dobbelsteyn, Peacocke, Blake, Crist, & Rashid, 2008).

GI and feeding issues are associated with great morbidity and mortality in this genetic condition. One study that examined the healthcare needs of individuals with CHARGE syndrome in the UK found that in just the first year of life, GI symptoms contributed to extended hospitalizations (26–230 days), 10–34 diagnostic procedures, and a trial of 10–28 prescribed medications (Anderzén-Carlsson, 2015). Although previously thought to be most highly prevalent in infancy and childhood, we have continued to learn more about the impact of existing and the development of new feeding and GI issues well into adolescence and adulthood (Bergman et al., 2010; Blake, Salem-Hartshorne, Daoud, & Gradstein, 2005; Dobbelsteyn, Marche, Blake, & Rashid, 2005; Dobbelsteyn et al., 2008; Hartshorne et al., 2016).

GI and feeding issues have been found to be so highly prevalent that "feeding difficulties/dysphagia" have been recently proposed as new "minor" diagnostic criterion in the clinical diagnosis of CHARGE syndrome (Hale et al., 2016). At least six of the clinical major and minor diagnostic criteria (cranial nerve dysfunction, choanal atresia/stenosis, cardiovascular malformation [i.e., vascular ring], orofacial cleft, trachea-eosophageal fistula, developmental delay) contribute directly to feeding and GI issues, highlighting the pervasiveness of these dysfunctions (Blake et al., 1998; Verloes, 2005). The structural anomalies, motor impairment, and oral sensory impairment all contribute to these issues, and are all potential treatment targets. The aim of this review is to comprehensively summarize the existing literature on the nature of GI and feeding dysfunction in CHARGE syndrome, including the pathophysiology, symptomology, and treatment options.

2 | METHODS

An electronic systematic search was conducted via PubMed using the following search terms: CHARGE syndrome and GI, feeding, reflux, or cranial nerve. There were no restrictions placed on article type or year of publication. Titles and abstracts were reviewed for relevance. Reference lists of identified articles were reviewed for inclusion of any additional relevant articles. The articles were summarized and divided into type of feeding or GI problem, from mouth to anus. The original list of articles was then reappraised to identify any missing topics.

3 | RESULTS

Ninety-seven articles were identified using the search strategy. Titles and abstracts were screened for relevance to the topic and any duplicates, which resulted in the exclusion of 49 articles. The remaining 48 articles' reference lists were reviewed for additional relevant articles. A final total of 71 articles were included for review. Their findings are summarized below, from head-to-toe. Table 1 displays a summary of the phenotypic characteristics of CHARGE syndrome,

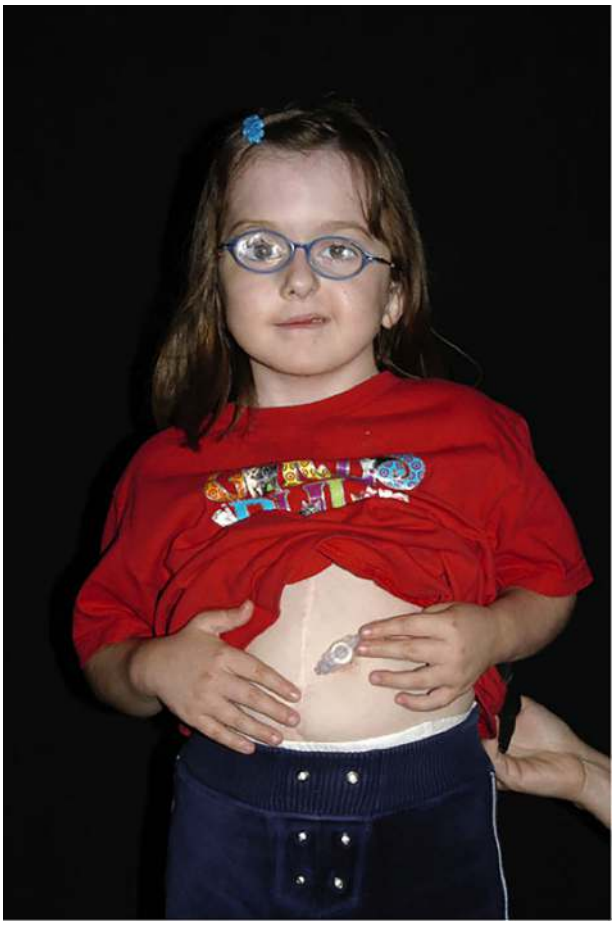

FIGURE 2 A child with CHARGE syndrome showing her gastrostomy tube button. Over 90% of individuals with CHARGE syndrome need tube feeding at some point in their life

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 malformation	• 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
Distinct facial features	• Over-crowded oral cavity (small mouth, macroglossia)	100%	• Swallowing difficulties • Choking hazard • Inability to properly manipulate food with tongue

their frequency in the CHARGE syndrome population, and their associated GI and feeding dysfunction. Table 2 summarizes the currently available treatment options for all GI and feeding difficulties in CHARGE syndrome.

3.1 | Sense of smell

The sense of smell plays an extremely important role in the perception of taste and overall enjoyment of food. In CHARGE syndrome, the incidence of olfactory bulb absence or hypoplasia has been reported to be over 80%, contributing to a reduced or completely absent sense of smell (Blake, Hartshorne, Lawand, Dailor, & Thelin, 2008; Chalouhi et al., 2005). Magnetic resonance imaging demonstrating hypoplastic or absent olfactory bulbs and sulci can therefore be a major diagnostic clue in aiding the clinical diagnosis of CHARGE syndrome (Blustajn, Kirsch, Panigrahy, & Netchine, 2008). Individuals may prefer strong tasting food as a result of their diminished/absent sense of smell.

TABLE 2 A summary of currently available treatment options for gastrointestinal and feeding difficulties, from head to toe, in CHARGE syndrome

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 over-stuffing[a]	• 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 left over 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

[a]See more helpful interventions identified by parents in Hudson et al. (2016).

3.2 | Craniofacial anomalies

Craniofacial surgeries are the third most common type of surgeries individuals with CHARGE syndrome will undergo in their lifetime. These surgical procedures include cleft lip/palate repair, choanal atresia repair and re-dilatations, tonsillectomy, and adenoidectomy (Blake et al., 2009). These structural anomalies and their associated surgical repairs, often negatively affect feeding and can delay the introduction of oral feeding (Samadi, Shah, & Handler, 2003).

Choanal atresia/stenosis, a blockage/narrowing of the nasal passage, is one of the major clinical diagnostic criteria of CHARGE syndrome. They can both disrupt respiration during sucking, and are often a major problem at birth, interfering with an infant's ability to feed (Dobbelsteyn et al., 2005). A CT scan or nasal endoscopy is often needed to assess the patency of the choanae. Repeat dilatations can be required for long-term management. Gastroesophageal reflux, a very common comorbidity in CHARGE syndrome (see section below), has been identified as a predictive factor of re-stenosis of the choanae after undergoing surgical repair of choanal atresia (Teissier, Kaguelidou, Couloigner, François, & Van Den Abbeele, 2008).

Cleft palate and/or lip are found in just under half of individuals with this genetic condition. This interferes with sucking behavior at birth, as individuals are unable to close off the nasal cavity.

Individuals often have a small mouth and enlarged tongue, leading to a crowded oral cavity (Sanlaville & Verloes, 2007). A recent study describing the clinical characteristics of Danish individuals with CHARGE syndrome found that 69% ($n = 9/13$) had a small mouth (Husu et al., 2013). This can lead to problems with sleep apnea and feeding (Trider et al., 2012; Trider & Blake, 2012). Ear-nose-throat (ENT) surgeons have been reported to be the number one specialty that follows individuals with CHARGE syndrome throughout their life, due to the high prevalence of head and neck dysfunction (Blake et al., 2005; Hartshorne et al., 2016). A recent case report described the success of an implanted hypoglossal nerve stimulator to treat refractory severe obstructive sleep apnea in an adolescent with Down syndrome (Diercks et al., 2016). This has not yet been described in CHARGE syndrome, but has great potential due to the high prevalence of cranial nerve dysfunction (see section below).

3.3 | Salivation

Excess salivation can be a persistent problem in CHARGE syndrome. A study in Sweden of 26 individuals with CHARGE syndrome found that a quarter ($n = 9/26$) experienced persistent drooling (Strömland, Sjögreen, Johansson, Ekman Joelsson, & Miller, 2005). In part, this is due to salivary dysphagia, the inability to swallow the large quantity of saliva produced each day due to swallowing abnormalities that are extremely common (Dobbelsteyn et al., 2008). This is also linked to the extensive cranial nerve dysfunction (see section below), as the three most important salivary glands are innervated by the facial nerve (submandibular and sublingual glands) as well as the glossopharyngeal nerve (parotid gland) (Blake et al., 2008). Salivary glands may also be found in abnormal locations, as one previous case report discussed the finding of a unilateral ectopic parotid gland in an individual with CHARGE syndrome (Ormitti, Ventura, Bacciu, Crisi, & Magnani, 2013).

Excessive secretions can interfere with feeding, as well as negatively impact social situations. It has also been shown to be a leading cause of postoperative events, as the excessive saliva can obstruct the airway and require continuous suctioning as the individual is waking from surgery (Blake et al., 2009). Attention to this issue is important as individuals undergo an average of 22 surgeries throughout their lifetime (Blake et al., 2009). It is imperative that multiple procedures be combined under one anesthetic wherever possible. Botulinum toxin A (Botox) injection into the salivary glands every 4–5 months has been shown to be an effective treatment option in reducing salivary secretions for some individuals, however this is not effective in everyone (Blake, Maccuspie, & Corsten, 2012).

3.4 | Aspiration

Aspiration is a common problem in CHARGE syndrome, due to the high prevalent swallowing abnormalities and excess salivation. A previous study found that 60% ($n = 18/30$) of individuals with CHARGE syndrome had aspiration confirmed by endoscopy, with 80% ($n = 24/30$) having abnormal swallowing, evidenced by pooling of secretions, poor food bolus mobility, and laryngeal dyscoordination (White, Giambra, Hopkin, Daines, & Rutter, 2005). Recurrent pneumonias should be a clue that leads to investigations (e.g., swallow and feeding studies) for aspiration. Respiratory aspiration has also been identified as a major cause of death seen in children and adolescents with CHARGE syndrome (Bergman et al., 2010; Sporik, Dinwiddie, & Wallis, 1997). Severe gastroesophageal reflux disease can also be a cause of aspiration in this syndrome. The presence of aspiration is often a major reason for exclusive tube feeding (Dobbelsteyn et al., 2008).

3.5 | Tube feeding

Gastrostomy, jejunostomy, and/or nasogastric tubes are used in over 90% of children with CHARGE syndrome (Bergman et al., 2011; Dobbelsteyn et al., 2008) GI surgeries (tube placement, G-button insertion, and change) are the number one surgeries in this genetic condition (Blake et al., 2009). As many individuals are dependent upon tube feeding in their early life, sometimes for upwards of years, or even indefinitely, the development of oral feeding skills is disrupted. Individuals often have aversion to certain food textures due to this delay of introduction of oral feeding (Dobbelsteyn et al., 2008).

3.6 | Packing and mouth over-stuffing

Packing, or pocketing of food into cheeks, and overstuffing food into one's mouth have been identified as pervasive and problematic feeding behaviors at mealtime in many individuals with CHARGE syndrome (Hudson, Colp, & Blake, 2015; Hudson, Macdonald, & Blake, 2016). It has been found to most often occur with bread/pasta type foods and can prolong mealtimes for over an hour. It is also common to find leftover food in cheeks hours after a meal has ended. Effective

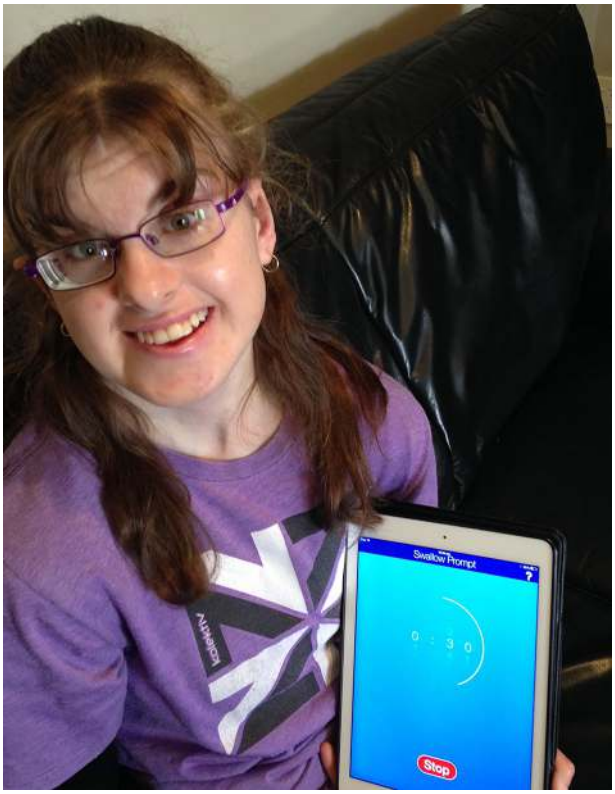

FIGURE 3 A teenager with CHARGE syndrome using an electronic application to remind her to swallow every 30 s during mealtime. This technique helped reduce her feeding issues with mouth over-stuffing and packing food into her cheeks

interventions identified by parents include using liquid chasers (e.g., water, puree) after taking bites of food, cutting food into small pieces, serving small amounts on the plate at a time, using an iPad timer application to remind to swallow (Figure 3), and allowing the individual to spit out a food bolus if unable to swallow (Hudson et al., 2016).

3.7 | Choking

Choking is unfortunately a common occurrence, due a combination of feeding and GI symptoms mentioned in this review article, including abnormal swallowing, pocketing food and over-stuffing, abnormal tongue movement, and cranial nerve dysfunction. Suck, swallow, breath, synchrony should be discussed as an important physiological developmental milestone (Hsu et al., 2014). A previous study identified that parents' number one concern with packing of food into cheeks and over-stuffing was the possibility of choking on food (Hudson et al., 2016). Choking has also been identified as a common cause of death after the neonatal period (Bergman et al., 2010). Close supervision during mealtimes, restriction of certain food types or textures, and practicing eating slowly may help reduce the risk of choking in this population. Anatomical abnormalities, such as vascular rings, can also contribute to choking. Therefore, new signs of choking in an individual with CHARGE syndrome warrants further work-up.

3.8 | Cranial nerve dysfunction

The most common cranial nerve abnormalities in CHARGE syndrome include cranial nerves (CN) V (trigeminal), VII (facial), VIII (vestibulocochlear), IX (glossopharyngeal), X (vagus), and XI (accessory) (Blake et al., 2008). These CN provide very important sensory afferent information that get integrated in brainstem swallowing programming centers, which then send out motor efferents to control the feeding sucking reflex (Abadie & Couly, 2013). Sucking, swallowing, chewing, biting, and licking can be absent, poor, hypersensitive, or completely aversive in CHARGE syndrome due to cranial nerve dysfunction. The trigeminal nerve (CN V) innervates the muscles of mastication and is responsible for sensation of the face. Abnormal function of this nerve can lead to dysfunctional chewing, increasing the risk of aspiration and pocketing, as discussed in the paragraphs above.

Esophageal dysmotility is a common issue due to cranial nerve dysfunction. Motility of a food bolus down the esophagus requires coordination of swallowing and ventilation, as well as appropriate peristalsis down the esophagus (Abadie & Couly, 2013).

Gagging should be assessed as an indication of neurological dysfunction, as cranial nerve IX is responsible for the afferent sensation pathway and cranial nerve X is responsible for the efferent motor response. A normal gag reflex would indicate that there is less risk of aspiration and stress, and would provide support for safe oral feeding. Neurological function has been shown to improve with age in CHARGE syndrome, which may result in some improvement in feeding difficulties (Blake et al., 2008). However, individuals must re-learn how to coordinate chewing and swallowing. Feeding therapy with a speech language pathologist, occupational therapist, or other clinician is essential for this re-learning process.

3.9 | Gastroesophageal reflux

Gastroesophageal reflux is extremely common in individuals with CHARGE syndrome, and as such has received a lot of attention in the published literature. The symptoms of reflux can often be characterized by spitting, vomiting, agitation, crying, disrupted sleep, and drawing up of knees onto the chest with crying (Dobbelsteyn et al., 2008). An epidemiological study of individuals with CHARGE syndrome in Canada found that the six individuals who had deceased all had suffered from reflux, of which five needed a gastrostomy tube due to the severity of the reflux (Issekutz, Graham, Prasad, Smith, & Blake, 2005). Another study found that GERD, combined with feeding and breathing difficulties, was a significant risk factor for early mortality in CHARGE syndrome (Bergman et al., 2010). Esophageal reflux has also been shown to be a significant predictor of longer hospital stays in this genetic disorder (Vervloed, Hoevenaars-van den Boom, van Ravenswaaij, & Ronald Admiraal, 2006).

Many individuals undergo surgery (Nissen fundoplication) in an effort to relieve reflux symptoms. Unfortunately, there is a high rate of failure and many individuals subsequently undergo the procedure two or three times (Kimber, Kiely, & Spitz, 1998). The predominant cause of

fundoplication failure has been found to be herniation into the posterior mediastinum. Even after surgery, many continue to need medical management of symptoms. A recent study of 44 children with CHARGE syndrome in the UK found that almost half ($n = 20$) were taking medication for reflux (Deuce, Howard, Rose, & Fuggle, 2012).

3.10 | Esophageal and cardiac structural defects

Structural defects such as a tracheoesophageal fistula can preclude normal swallowing early in life (Naito et al., 2007). This type of defects needs immediate surgical correction. Laryngeal and laryngo-tracheso-phageal clefts are also found in CHARGE syndrome and can predispose the individual to aspiration (Johnston, Watters, Ferrari, & Rahbar, 2014; Leboulanger & Garabédian, 2011). Cardiac malformations (i.e., vascular rings) have been identified as a cause of swallowing difficulties in individuals with CHARGE syndrome, as they can compress the esophagus and prevent bolus movement. Cardiac conditions can also worsen feeding problems, as infants fatigue easily, have inefficient feeding, and often have resulting failure to thrive (Corsten-Janssen, van Ravenswaaij-Arts, & Kaputsa, 2016). Occasionally individuals with CHARGE syndrome can have a congenital diaphragmatic hernia, which can lead to poor feeding and failure to thrive (Stoll, Alembik, Dott, & Roth, 2008).

3.11 | Abdominal pain and bloating

Abdominal pain and bloating are common and persistent issues throughout the lifespan in CHARGE syndrome. Individuals often experience abdominal gurgling and decreased abdominal muscle tone. Pain can be very difficult to assess in individuals with CHARGE syndrome as communication is often supported with multiple non-vocal methods, including sign language, gestures, or picture exchange (Dammeyer, 2012; Hartshorne et al., 2016; Salem-Hartshorne & Jacob, 2005). The CHARGE Non-Vocal Pain Assessment scale can be completed by parents when they think their child is in pain, to help them objectively quantify and compare pain that they think their child is experiencing (Stratton & Hartshorne, 2016).

Parents have identified abdominal massage as an effective method to provide relief to abdominal pain (Dobbelsteyn et al., 2005). Treatment options identified for Irritable Bowel Syndrome (IBS), such as following the low FODMAP (fermentable oligosaccharides, disaccharides, mono-saccharides, and polyols) diet and taking probiotics, may help provide symptomatic relief in individuals with CHARGE syndrome as well. A dietitian can be a very valuable addition to the healthcare management team in order to address diet alteration for symptom management.

3.12 | Late dumping syndrome

Late dumping syndrome is a common issue in CHARGE syndrome. Symptoms occur 1–3 hr after a meal and are a manifestation of hypoglycemia and include perspiration, palpitations, hunger, weakness, confusion, tremor, and syncope (Tack, Arts, Caenepeel, De Wulf, & Bisschops, 2009). Glucose (i.e., carbohydrates) in the small intestine is a stimulus for the secretion of insulin, and in late dumping syndrome there is a quicker than usual transit of carbohydrates into the small intestine, causing excessive insulin and resulting hypoglycemia. It most commonly appears in those who have had esophageal surgery, such as a Nissen fundoplication, which many individuals with CHARGE syndrome undergo due to persistent pharmacological refractory gastroesophgeal reflux disease. However, it can also occur in individuals who are naïve to surgery.

Treatment options focus on the diet, including consuming smaller amounts and reducing simple carbohydrates (e.g., sweets, white bread). This may be difficult to implement and can warrant help from a dietitian and feeding therapist as many individuals have texture-limited diets, or have feeding behaviors that can interfere with this (e.g., mouth over-stuffing). Implementing these treatment suggestions for late dumping syndrome can conversely positively improve mouth over-stuffing and food pocketing behaviors, as well as help prevent obesity, which is highly prevalent in the later years in this population.

3.13 | Bone health

As individuals transition from tube to oral feeding, or for those who are 100% oral feeders from birth, extra attention needs to be paid to ensure a balanced and varied oral diet that provides an adequate intake of nutrients. This may be difficult due to limitations by sensory difficulties and motor impairment. A dietitian may be a valuable addition to the individual's healthcare team. A previous study found that 41% and 87% of the CHARGE syndrome study population did not meet their recommended daily intake of calcium and vitamin D, respectively, (Forward, Cummings, & Blake, 2007). This can predispose the individual to be at a higher risk for poor bone health. Bone health issues have recently been identified as the most common new medical issue that appears in adolescence and adulthood, occurring in 40% of the study population (Hartshorne et al., 2016). Vitamin-D rich foods and supplementation of 1,000 international units of vitamin D should be recommended to individuals with CHARGE syndrome. Weight bearing activities should also be recommended, as it can help increase bone mineral density and prevent osteoporosis.

3.14 | Obesity

As infants, individuals most commonly struggle with failure to thrive, and the support is focused on increasing feeding to facilitate adequate nutrition and growth. As an individual moves into his/her teenage years and beyond, the focus on promoting increased feeding may need to be decreased as issues with obesity may arise. Individuals with CHARGE syndrome have also been found to be less active than their peers, which increases the risk of having a higher body mass index (BMI) (Forward et al., 2007). This can be difficult to achieve, as for many the failure to thrive can persist a prolonged period of time. Furthermore, problematic feeding behaviors such as mouth over-stuffing can make this difficult to achieve. However, the negative health consequences of obesity, such as the increased risk of metabolic syndrome, cannot be overlooked.

3.15 | Constipation

Constipation has been identified as a common problem in CHA-RGE syndrome, often necessitating pharmacological treatment

(Anderzén-Carlsson, 2015). A recent study in the UK found that one-fifth (n = 9/44) of their study population was taking medication to treat constipation (Deuce et al., 2012). Another study in the UK that examined infants with CHARGE syndrome found that troubles with constipation caused a need for medication, enemas, and even mechanical stimulation with a rectal probe (Anderzén-Carlsson, 2015). Causes of constipation in this genetic disorder are multifactorial, including abnormal innervation of the GI tract, gastrostomy and jejunostomy tube feeding, a diet limited in texture and food type, as well as maladaptive behaviors around toileting (Hudson, Trider, & Blake, 2017; Hudson, Macdonald, Friedman, & Blake, 2017; Macdonald, Hudson, Ratcliffe, Bladon, & Blake, 2016). Furthermore, children with CHARGE syndrome who are tube fed have been found to have significantly more problems with constipation than those who are orally fed (Macdonald et al., 2016).

3.16 | Enteric nervous system dysfunction

The GI system in zebrafish models of CHARGE syndrome (*CHD7* gene knockouts) has been shown to have decreased number of enteric nerve branches and motility, with delayed emptying of the GI tract (Cloney et al., 2016). This has not been studied in humans yet.

3.17 | Feeding behaviors

Repetitive behaviors are common in CHARGE syndrome, which include behaviors like having to eat specific foods at specific meals, eating in the same order each time, needing the plate to be completely empty, and more (Bernstein & Denno, 2005). Behaviors may be self-stimulatory and self-regulatory, due to the significant sensory impairments from cranial nerve dysfunction, maladaptive behaviors, tics, or obsessive-compulsive-like behaviors. Adolescents and adults with CHARGE syndrome receive mental health diagnoses of obsessive-compulsive disorder, anxiety disorder, tics/tourette syndrome, and ADHD (Blake et al., 2005; Hartshorne et al., 2016). Therefore, adapting mealtime routines for each individual's own unique behavior difficulties can help reduce feeding difficulties.

Compensatory behaviors may also be expressed when experiencing discomfort, as many individuals with CHARGE syndrome have delayed speech and hearing development, and may only be able to communicate through sign language or gestures. Therefore, certain gestures or behaviors may be the only way in which discomfort from constipation, bloating, reflux, or any other abdominal pain are expressed. Behavior is often an effort to adapt to the significant sensory impairments these individuals face, and can be related to problems with arousal and self-regulation (Blake & Prasad, 2006; Brown, 2005; Graham, Rosner, Dykens, & Visootsak, 2005; Hartshorne et al., 2005; Smith, Nichols, Issekutz, & Blake, 2005).

3.18 | Adolescents and adults

Feeding difficulties have been reported in nearly 90% of adolescents and adults with CHARGE syndrome living in Canada (Issekutz et al., 2005). Abdominal colic/migraine is the most common new feeding issue that arises after childhood (Blake et al., 2005; Searle, Graham, Prasad, & Blake, 2005). The majority of adolescents and adults have no independence in cooking, contributing to further feeding difficulties and the need for close supervision and help (Blake et al., 2005; Hartshorne et al., 2016). Adolescents and adults have reported feeding difficulties to be a major source of limitation to daily activities (Hartshorne et al., 2016). New mental health diagnoses that adolescents and adults with CHARGE syndrome have received, such as obsessive-compulsive disorder and eating disorders, can greatly impair mealtime and nutrition. Last, behavioral concerns (tactile defensiveness, aggressiveness/outbursts) become more apparent in later years and can also lead to problems with food textures and finishing meals.

4 | GAPS AND FUTURE RESEARCH

Cranial and enteric nerve dysfunction is the most promising area for future research and treatment options for feeding and GI dysfunction in CHARGE syndrome. Despite current options for surgical repair of structural anomalies and medication management of excess salivation, gastroesophageal reflux, abdominal pain, and constipation, there exist continual lifelong feeding and GI issues that are not adequately controlled. There are currently very few treatment options for cranial nerve dysfunction and gut motility, which contribute to almost every type of feeding and GI issue in CHARGE

TABLE 3 Recommendations for clinical practice in assessing feeding and gastrointestinal difficulties in CHARGE syndrome

Identification of feeding and GI dysfunction
Parents, researchers, and clinicians can use the validated CHARGE syndrome checklist (CL) Trider et al. (2017) and the feeding assessment scale for CHARGE syndrome (in progress) to bring attention to these important issues. These issues can appear for the first time at any age in CHARGE syndrome (infancy, childhood, adolescence, adulthood).
Multidisciplinary team approach
Continual evaluation of feeding and gastrointestinal symptoms should be a part of the standard care of all individuals with CHARGE syndrome. Multiple medical specialties (e.g., ENT, speech language pathology, feeding therapy) are needed, and should be included in the healthcare team early on in an individual's life before feeding and GI symptoms worsen.
Individualized treatment
Just as the phenotypic manifestations of CHARGE syndrome exist on a spectrum from very mild to severe, so do the feeding and GI difficulties experienced in this genetic disorder. Individuals may fail many treatment options before they find symptom relief. Multiple modalities of treatments (medical, surgical, behavioral) are needed to optimize feeding and GI outcomes.

syndrome. This gap needs to be addressed in future studies. Research studies analyzing the innervation of the GI tract in zebra fish models of CHARGE syndrome are ongoing (Cloney et al., 2016). Future studies should continue to analyze the enteric nervous system and motility of the CHARGE GI tract, as well as investigate the gut microbiome. Last, research studies should continue to examine the impact of GI and feeding issues on the lives of adolescents and adults with CHARGE syndrome, as individuals with this genetic disorder are now living much longer.

5 | SUMMARY

GI and feeding difficulties are pervasive and ongoing issues in CHARGE syndrome, carrying great morbidity and mortality. Similar to the many clinical features of CHARGE syndrome, there exists a wide range of symptomatology, from very mild to severe. Individuals can experience problems anywhere along the entire GI tract. Furthermore, these difficulties can appear for the first time from infancy to adulthood. Recommendations for addressing GI and feeding difficulties in this genetic disorder are summarized in Table 3. As medical and surgical interventions improve, and the expected lifespan of individuals with CHARGE syndrome lengthens, it is important we continue to research the underlying pathophysiology and potential treatment options for feeding and GI dysfunction in this genetic disorder.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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