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ORIGINAL ARTICLE

Oropharyngeal Dysphagia in Infants and Children with Infantile Pompe Disease

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Abstract Pompe disease is a rare genetic progressive neuromuscular disorder. The most severe form, infantile Pompe disease, has historically resulted in early mortality, most commonly due to cardiorespiratory failure. Treatment with enzyme replacement therapy (ERT) using alglucosidase alfa (Myozyme®) has extended the lifespan of individuals with this disease. With the introduction of ERT and the resultant improved survival, dysphagia is being encountered clinically with increasing regularity though systematic data remain unavailable. We retrospectively studied the oropharyngeal swallowing of 13 infants and children with Pompe disease using videofluoroscopy before initiation of ERT, allowing for baseline swallow function to be established in an untreated cohort. Dysphagia was present in all 13 subjects, even in a participant only 15 days old. Oral stage signs were present in 77%, most frequently a weak suck in 69%. Pharyngeal stage signs were present in 100%, including a pharyngeal swallow delay in 92% and pharyngeal residue in 77%. Airway invasion was present in 76.9% of subjects, including penetration in five (38.46%) and silent aspiration in an additional five (38.46%). No relationship in the relative involvement of swallowing, gross motor function, and cardiac disease appeared to be present.

Keywords Infantile Pompe disease · Oropharyngeal dysphagia · Aspiration · Glycogen storage disease type I · Acid maltase deficiency · Enzyme replacement therapy · Deglutition · Deglutition disorders

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Introduction

Pompe disease, also known as glycogen storage disease type II and acid maltase deficiency, is a rare autosomal recessive neuromuscular disease that occurs due to a deficiency of the lysosomal enzyme acid α glucosidase (GAA). A complete lack of GAA causes infantile Pompe disease, the most serious and devastating form of the condition. Infants with Pompe disease usually present by age 2 months with hypertrophic cardiomyopathy, extreme weakness, decreased muscle tone, and feeding/swallowing difficulties. Before recent advances in the medical treatment of this condition, death almost invariably occurred in the first year of life [1–5].

Enzyme replacement therapy (ERT) provides patients with Pompe disease with an exogenous form of GAA they are lacking. Alglucosidase alfa (Myozyme®, Genzyme, Cambridge, MA) was approved in 2006 for commercial use in North America and the European Union as the first treatment for this disorder [6–8]. Clinical trials using

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recombinant human acid α glucosidase (rhGAA) derived from Chinese hamster ovary cells and transgenic rabbit milk have shown improvement in overall survival rate, ventilator-free survival, degree of cardiac disease, and motor development in infantile Pompe disease. Cardiac response, in particular, is dramatic and improvement in cardiomyopathy is noted even in advanced cases. Skeletal muscle response is more variable [9–16].

As children with infantile Pompe disease are now living longer due to ERT, the need to identify complications or other factors that may influence outcome has developed. For example, clinical issues that have been reported in survivors of this illness include decreased bone density and increased fracture risk [17], hearing loss [18], risk of cardiac arrhythmias [19], and increased anesthesia risk [20]. More recently, we reported on language and speech function in 12 subjects. Disorders in language and/or speech were found in all 12 participants at some point during the course of the study. Overall, delays in language tended to improve with time, while speech disorders were encountered more commonly, were often severe, and appeared to be motor in nature [21].

We now focus our attention on the description of oropharyngeal swallow function in 13 untreated subjects with infantile Pompe disease. Although dysphagia is now routinely encountered clinically and has been reported as part of practice guidelines for this population [22], to our knowledge no data on swallow function are available in the literature. Our primary purpose was to determine baseline oropharyngeal swallowing function in a group of untreated infants and children with Pompe disease. Our secondary purpose was to explore correlations in terms of severity of involvement between oropharyngeal swallowing, gross motor function, and hypertrophic cardiomyopathy.

Methods

The medical records of 13 infants and children with infantile Pompe disease who were enrolled in various clinical trials to study the effects of ERT at a tertiary care center were reviewed. All studies were approved by the Institutional Review Board and informed consent was obtained from each participant's parent/guardian. Inclusion criteria included a diagnosis of infantile Pompe disease (as defined by the onset of signs of Pompe disease by 12 months of age and skin fibroblast GAA activity $\leq$1% of the normal mean) and completion of a videofluoroscopic swallow examination (VFSE) prior to or within 30 days of starting ERT. VFSEs were conducted as part of routine clinical care by speech-language pathologists (SLPs) with clinical privileges and expertise in pediatric swallowing assessment.

Medical records were reviewed for documentation regarding feeding and swallowing status based on subjective assessment of caregivers, method(s) of receiving nutrition (e.g., oral diet, tube feeding, or a combination), clinical diagnosis of failure to thrive (FTT), swallowing signs present on VFSE, and overall severity of dysphagia. Oral stage signs assessed included a weak suck, slow preparation, tongue thrust, oral dysmotility, oral residue, lip incompetence, and oral disorganization. Pharyngeal stage signs assessed included nasal regurgitation, delayed initiation of swallow, pharyngeal residue, upper esophageal sphincter (UES) dysfunction, and airway invasion (i.e., penetration and aspiration). Penetration was defined as entry of the bolus into the larynx to the level of the vocal folds, while aspiration occurred with entry of the bolus past the level of the vocal folds into the trachea. Aspiration was further described as audible if a cough occurred and as silent if no cough was elicited. Severity of dysphagia was determined to be mild, moderate, or severe based on clinical judgment of each subject's swallowing signs and their severity, as well as post-VFSE swallowing recommendations (e.g., normal diet, modified diet, or nonoral nutrition).

VFSEs were completed jointly by a SLP and a radiologist following hospital protocol using videoradiography to study the anatomy and physiology of the oropharynx, larynx, and UES during the oral, pharyngeal, and cervical esophageal stages of swallowing. The purposes of the exam were to determine the structure and function of the swallowing mechanism, swallowing safety, the benefit of compensatory swallow strategies, and an optimal feeding plan. The standard procedure involves administration of various barium boluses, including liquid barium in various consistencies, pureed foods, and solids. Participants were placed in a Tumble Form Feeder Seat® to allow for a feeding position appropriate to developmental age and motor function (e.g., infants semireclining, toddlers upright). A lateral radiographic image was viewed during real-time swallowing as the participants were presented barium consistencies by various methods of presentation (e.g., bottle, cup, and spoon). The specific item(s) administered for each patient were tailored for developmental age, feeding abilities, and food exposure.

Baseline gross motor function was determined by a physical therapist with expertise in pediatrics using the Alberta Infant Motor Scales (AIMS) [23]. The AIMS is a norm-referenced observational measure of infant motor performance which assesses the sequential development of motor milestones from term to independent walking in terms of the progressive development and integration of antigravity muscular control in prone, supine, sitting, and standing positions. The AIMS was developed to discriminate infants exhibiting immature and atypical motor performance from those exhibiting normal development and to

evaluate small increments in performance that occur over time as a result of maturation or intervention. The AIMS is appropriate for use from birth to 18 months of age and provides percentile rank for age. Age equivalencies were determined based on the age at which 50% of children would achieve the associated raw score. For subject 3, AIMS score was calculated from individual items scored during administration of the Gross Motor Function Measure (GMFM) [24].

Degree of cardiac hypertrophy was determined by two-dimensional echocardiography using the area-length method [25]. Hypertrophic cardiomyopathy was defined as a left ventricular mass index (LVMI) greater than or equal to 65 g/m^2. Echocardiograms were interpreted by a pediatric cardiologist. LVMI values were converted into z-scores [26].

Results

Participants

Thirteen subjects, seven males and six females of a variety of ethnicities, participated in the study. Twelve subjects (92%) were delivered following full-term pregnancy. Mean age at time of VFSE was 7.55 months (SD = 4.15, range = 0.53–16.1) and mean age upon initiation of ERT was 7.18 months (SD = 4.45, range = 0.50–16.1). Eleven subjects (85%) received VFSE prior to or within 1 day of the initiation of ERT. The two remaining subjects each received one dose of ERT before the completion of VFSE. Subject 11 received VFSE 18 days after starting treatment and subject 12 had VFSE 25 days after starting treatment. Failure to thrive (FTT) was diagnosed in eight subjects (62%). Subjective feeding and/or swallowing difficulty were reported by caregivers in seven participants (54%). At the time of the VFSE, eight subjects (62%) were receiving oral nutrition, while five participants (38%) were receiving nasogastric tube (NGT) feedings due to feeding difficulties, decreased weight gain, evidence of dysphagia/aspiration, or the need for nutritional access during hospital transfer. Individual demographic data are given in Table 1.

Swallowing

Swallowing signs and their frequency of occurrence in our cohort during VFSE are found in Fig. 1.

Oral Stage

Oral stage deficits were present in 10/13 subjects (77%). The most common oral stage signs were a weak suck in 9/13 (69%) and slowness in oral stage transit in 8/13 (62%). Oral residue was present in 4/13 (31%). Tongue thrust, oral dysmotility, lip incompetence, and oral disorganization were all exhibited in 3/13 subjects (23%). Three participants, subjects 2, 4, and 13, had normal oral stage function. Subjects 4 and 13 were the oldest subjects and the only participants able to sit independently and maintain head control in independent sitting, perhaps suggesting postural control which may be supportive of oral stage function.

Table 1 Subject demographic data

Subject	Sex	Ethnicity	Gestational age (weeks)	Age at VFSE (months)	Age at first ERT (months)	FTT	Subjective feeding difficulty	Presence of NGT
1	M	C	40	2.97	2.9	+	−	−
2	M	C	39	0.53	0.5	−	−	−
3	M	AA	37	5.57	5.7	+	+	−
4	M	AA	37	16.10	16.1	−	+	−
5	F	C	37	8.27	7.0	+	+	+
6	F	C	33	8.30	N/A[a]	+	−	+
7	M	A	37	5.53	4.6	+	+	+
8	F	I	40	9.33	9.4	+	+	−
9	F	H	38	7.33	5.4	−	−	−
10	F	EA	40	3.57	3.7	−	−	+
11	M	AA	40	9.37	10.0	+	+	−
12	M	H	35	8.03	7.4	−	−	+
13	F	AA	40	13.17	13.4	+	+	−

M male, *F* female, *C* Caucasian, *AA* African American, *A* Asian, *I* Indian, *H* Hispanic, *EA* Eastern Asian, *VFSE* videofluoroscopic swallow examination, *ERT* enzyme replacement therapy, *FTT* failure to thrive; +, present; −, absent, *NGT* nasogastric tube

[a] Subject died before enzyme replacement therapy

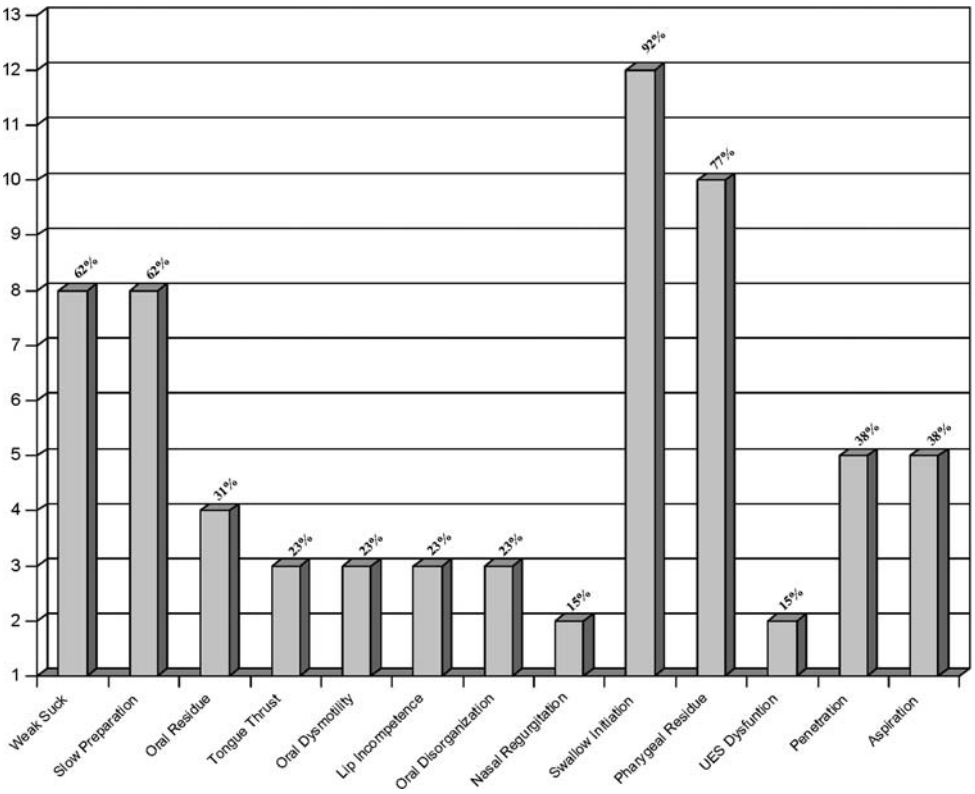

Fig. 1 Oral and pharyngeal swallow signs determined via the videofluoroscopic swallow examination (VFSE) in a group of 13 participants with infantile Pompe disease. The *x* axis details the specific swallowing signs observed and the *y* axis details the number of subjects with each sign. *UES* upper esophageal sphincter

Pharyngeal Stage

Pharyngeal stage deficits were present in all 13 subjects (100%). A delay in the initiation of the pharyngeal swallow was the most common swallowing sign and present in 12/13 participants (92%). Initiation at the level of the valleculae was seen in seven subjects (54%) and at the pyriform sinuses in five (38%). An abnormal amount of post-swallow pharyngeal residue was present in 10/13 (77%). This amount was judged to be mild in four (31%), moderate in five (38%), and profound in one (8%). UES function was reported to be normal in 9/13 (69%). Abnormal UES function was reported in two cases (15%), and in two instances UES function was not described (15%). Nasal regurgitation was present in 2/13 (15%).

Airway Invasion

Airway invasion was observed in 10/13 participants (76.9%). Penetration was present in five subjects (38.46%) and aspiration occurred in an additional five cases (38%). All episodes of aspiration occurred silently. There was 100% agreement between speech pathology and radiology on whether airway invasion, penetration, and/or aspiration occurred. In one instance, however, radiology reported only the lack of aspiration while speech pathology documented airway invasion secondary to penetration. Thus, if considered most strictly, agreement was 92% between speech pathology and radiology on these airway invasion observations.

Dysphagia Severity/VFSE Recommendations

Dysphagia severity was mild in five subjects (38%), moderate in three (23%), and severe in five (38%). Following completion of the VFSE, a recommendation of nil per os (NPO) was made in 5/13 (38%). In one of these instances, dysphagia severity was only mild but the subject required continuous bilevel positive airway pressure (BI-PAP) which precluded oral intake. An oral diet was recommended in 8/13 (62%). In 5/13 (38%), the feeding plan was changed based on VFSE results and recommendations, including use of thickened liquids in three cases and implementation of NPO in two.

Gross Motor Function

Baseline assessment of gross motor function was completed in 12/13 subjects using the AIMS. For subject 3, the AIMS score was calculated from individual items scored during administration of the GMFM. Eleven of 13 subjects (85%) had an AIMS percentile less than 5th. Subjects 1 and

2 both scored between the 10th and 25th percentile. AIMS age equivalencies were calculated as previously described in the Methods section. AIMS age equivalencies ranged from "less than newborn" to 3.66 months, while chronological ages ranged from 0.47 to 16.33 months. If AIMS age equivalencies of "less than newborn" or "newborn" are considered to be an age equivalency of 0, the mean AIMS age equivalency was 1.65 months (SD = 1.35). In contrast, the mean chronological age at the time of AIMS testing was 7.27 months (SD = 4.34).

Cardiac Mass

Baseline hypertrophic cardiomyopathy was present in 12/13 (92%) subjects. Only subject 4 had normal cardiac LV mass. In the 12 subjects with hypertrophic cardiomyopathy, the mean LVMI was 448.36 g/m^2 (SD = 318.96) and the mean z-score was 11.58 (SD = 5.33).

Post Hoc Analyses

Fisher exact tests were used to test the independence of airway invasion (i.e., penetration and aspiration) and other swallowing signs. P values were set at 0.05 for statistical significance. All comparisons were found to be insignificant except for oral dysmotility and aspiration ($p = 0.04$) and pharyngeal residue and aspiration ($p = 0.02$). These data suggest that aspiration may be more likely in individuals with these swallowing signs.

Discussion

Oropharyngeal dysphagia is associated with a number of unwanted health outcomes, including malnutrition, dehydration, pulmonary consequences such as aspiration pneumonia, weight loss, and slowed or stopped weight gain. The effect of aspiration on pulmonary function in patients with prominent cardiopulmonary disease is of particular concern, especially considering cardiopulmonary disease is the most common cause of death in infantile Pompe disease. Exacerbating pulmonary disease in this gravely ill population with aspiration is a serious concern, especially when the lack of protective mechanisms in response to aspiration exhibited by our cohort and the prominent respiratory hypotonia known to be present in individuals with Pompe disease are considered. Post hoc analyses revealed that aspiration occurred more commonly in patients who exhibited oral dysmotility and pharyngeal residue. This provides some limited suggestion that patients who exhibit these swallowing signs may be at increased aspiration risk, even in the absence of aspiration during VFSE.

The pathophysiology of dysphagia in these subjects and other individuals with infantile Pompe disease is unknown. Myopathy of the bulbar musculature on which oropharyngeal swallowing is dependent is one possible explanation. Although Pompe disease has traditionally been considered to primarily affect the cardiac and skeletal muscles, there is evidence of bulbar muscle involvement as well. For example, we recently described speech disorders in children with Pompe disease and postulated that they could be at least partially due to lower motor neuron involvement resulting in weakness and flaccidity [21]. Such weakness may also be expected to have a negative influence on the swallowing mechanism and may provide a partial explanation for the pathophysiology of dysphagia in this population. In addition, respiratory hypotonia, including diaphragmatic weakness, is a hallmark feature of Pompe disease and difficulty coordinating respiration with swallowing is another possible mechanism contributing to dysphagia in this population. Further investigation will be needed to support, or refute, these preliminary hypotheses.

We attempted to determine if any relationships were present between oropharyngeal swallowing, gross motor function, and hypertrophic cardiomyopathy in the subjects examined in the present study. Overall, several observations can be made. Swallowing, gross motor function, and cardiac mass were all commonly disordered, often severely, in this cohort of 13 untreated subjects. In addition, there appeared to be little correlation between these three areas affected in infantile Pompe disease in individual participants. That is, performance in one area did not appear to have predictive value in the other areas studied. For example, subject 4 was the only participant who did not have cardiac involvement. This subject also only had mild dysphagia and intact oral stage function. However, gross motor function was affected much more severely as he was functioning below the 5th percentile and at age equivalency of 3.36 months, even though his chronological age at the time of testing was 16.33 months. Somewhat similarly, subject 2, our youngest participant who started ERT earliest in the course of his illness, also had mild dysphagia with intact oral stage function and was functioning at a higher level in terms of gross motor function (i.e., >10th percentile) than most of the rest of the cohort. However, this subject had substantial cardiac burden, with a LVMI of 305.7 (z-score = 10.9). Overall, our findings suggest that determining correlations between the severity of oropharyngeal swallowing, gross motor function, and hypertrophic cardiomyopathy was not possible in this small group of subjects. Also, untreated children with Pompe disease seem to be a heterogeneous group in terms of the severity and distribution of initial motor system involvement, particularly with regard to swallowing, and that predicting function in one motor area based on function in another is ill-advised.

Considering the high incidence of dysphagia, the common finding of silent aspiration, and the grave nature of illness in infantile Pompe disease, routine referral for swallowing assessment, including VFSE, seems prudent upon diagnosis and as needed, such as when a diagnosis of FTT is made or feeding/swallowing difficulties are reported by caregivers. In the present study, of the eight subjects diagnosed with FTT, seven had penetration or aspiration (88%). Of the seven subjects with subjective complaint of dysphagia, five also had airway invasion (71%). An interdisciplinary approach to swallowing problems in pediatrics has been reported to be beneficial [27] and is recommended for this complex population.

There are several limitations to this study which provide opportunity for future research. Overall, swallow function was crudely measured and future studies should increase sophistication in this respect. Use of a standard protocol during VFSE is planned in future prospective studies. In addition, this study does not provide any information on the effects of ERT on swallowing. It is already known that response to this treatment is different across muscle types (e.g., cardiac vs. skeletal muscles). The effect of ERT on the bulbar muscles on which swallowing depends remains unknown and is an important area for future research. Research in this area would also benefit from administration of clinical feeding and oral-motor examinations in a standard fashion. Infants and children with this disease commonly present with drooling, hypotonia, an open mouth posture, tongue protrusion, and macroglossia, and these findings require further study [21]. Other limitations of the study include its retrospective, descriptive nature; the limited number of data points collected; the lack of experimental control; and the lack of an age-matched control group of other chronically ill children without Pompe disease. Despite these limitations, we believe that these results are an important initial contribution to the understanding of oropharyngeal dysphagia in infants and children with Pompe disease, which will ultimately lead to improved clinical management of this challenging patient population.

In conclusion, we have described baseline oropharyngeal swallowing function using VFSE in 13 individuals with infantile Pompe disease prior to initiation of ERT. To our knowledge, this is the first systematic description of dysphagia in this population. All participants had at least one sign of oropharyngeal dysphagia and both the oral and pharyngeal stages of swallowing were typically affected. The most common swallowing signs in this cohort were a delay in the initiation of the pharyngeal swallow (92%); pharyngeal residue (77%); airway invasion (77%), which included an equal number of participants with penetration and aspiration; weak suck (69%); and slowness in oral stage transit (62%). Oropharyngeal dysphagia in general and aspiration in particular have considerable clinical implications for this complex population and we recommend routine swallowing assessment, including the use of videofluoroscopy, in infants and children with Pompe disease.

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