I, Alana Cecchi, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Analysis of Parental Perception of Swallowing and Voice in Infants and Children with Pompe Disease

Student's name: Alana Cecchi

This work and its defense approved by:

Committee chair: Thomas Burrows, MD
Committee member: Laurie Bailey, MS
Committee member: Nancy Doan Leslie, MD
Committee member: Claire Miller, PhD
Analysis of Parental Perception of Swallowing and Voice in Infants and Children with Pompe Disease

A thesis submitted to the Graduate School of the University of Cincinnati in partial fulfillment of the requirements for the degree of Master of Science

In the Department of Pediatrics of the College of Medicine

2011
by

Alana Cecchi
B.S. Michigan State University, East Lansing, MI

Committee Chairperson: T. Andrew Burrow, M.D.

Committee Members:

Laurie Bailey, M.S.
Claire Miller, Ph.D.
Nancy Leslie, M.D.
Pompe disease is an autosomal recessive lysosomal storage disease caused by a deficiency of the enzyme acid α-glucosidase (GAA). It is a heterogeneous neuromuscular condition which is classified into several different phenotypes based on the age of onset, severity of condition, and average age of death. If untreated, the most severe form typically results in death within the first year of life. With the advent of enzyme replacement therapy for Pompe disease, clinical manifestations of oropharyngeal swallowing and voice dysfunction have become increasingly apparent as individuals with Pompe disease are living longer. This study investigated the parental perspective of feeding, swallowing, and voice dysfunction in a cohort of 15 infants and children with Pompe disease using a parent questionnaire. Results indicated clinical signs and symptoms of oropharyngeal dysfunction reported in 63% of our cohort. Feeding-related quality of life issues were reported by 50% of parents/caregivers. Voice quality reportedly affected the overall well-being and development in 86% of the study population. This study documents the significance of feeding, swallowing, and voice dysfunction experienced by infants and children with Pompe disease.
# TABLE OF CONTENTS

ABSTRACT ii

TABLE OF CONTENTS iv

LIST OF TABLES AND FIGURES v

CHAPTER I: INTRODUCTION 1

CHAPTER II: METHODS 3
   Recruitment/Participants 3
   Instrument 4
   Data Analysis 5

CHAPTER III: RESULTS 5
   Oropharyngeal Swallowing Dysfunction 6
   Voice Dysfunction 8

CHAPTER IV: DISCUSSION 12

REFERENCES 20

APPENDIX A 22
LIST OF TABLES AND FIGURES

Table 1: Demographics of individuals with Pompe disease 6
Table 2: Swallowing dysfunction resulting from oral motor deficits 7
Figure 1: Impact of voice dysfunction on child’s communication 11

and quality-of-life
CHAPTER I: INTRODUCTION

Pompe disease (glycogen storage disease type II or acid maltase deficiency) is an autosomal recessively inherited lysosomal storage disease, resulting from defective and insufficient activity of the enzyme acid α-glucosidase (GAA) due to mutations in GAA. Decreased catalytic activity and/or instability of GAA leads to abnormal glycogen accumulation within the lysosomes of various tissues, including skeletal and cardiac muscle, hepatic tissue, and central nervous system, to varying degrees depending upon the phenotype. The incidence of this disease varies from 1/14,000 to 1/300,000 depending upon the patient population [1, 2].

Pompe disease is a heterogeneous condition that is classified into several different phenotypes, including classic infantile Pompe disease, non-classic infantile Pompe, childhood or juvenile Pompe, and adult-onset Pompe, based on age of onset, severity of organ involvement, and average age of death. The classic infantile form is the most severe and usually presents by age 1-2 months with cardiomyopathy, hypotonia, progressive muscle weakness, failure to thrive, feeding, and respiratory difficulties. A later-onset childhood form, inconsistently referred to as childhood or juvenile Pompe disease, usually presents after infancy and typically does not include severe cardiomyopathy. If left untreated, the classic infantile form progresses rapidly and usually results in death within the first year of life from cardiorespiratory failure [2-5].

With the advent of treatment with enzyme replacement therapy (ERT) using recombinant human acid α-glucosidase (GAA) (alglucosidase alfa; Myozyme®)[6], improvements in survival and stabilization of the disease have been observed. Specifically, ERT has led to improvements in invasive ventilation-free survival, cardiomyopathy indices, and improvements in motor development [3, 7-9]. Consequently, infants and children diagnosed with Pompe disease are
living longer. As a result, additional clinical manifestations of the disease have become more apparent. Recent studies and anecdotal observations have identified significant issues with feeding, swallowing, and voice in patients with Pompe disease [10, 11]. To date, studies examining the exact nature of these issues in infants and children with Pompe disease have primarily focused on descriptions of the physiologic causes of speech, language, and swallowing disorders in this population. Such studies have concluded that individuals with infantile Pompe disease are at high risk for developing speech and swallowing disorders [10, 11]. However, these studies are limited in describing the clinical characteristics, the physical distress and emotional impacts experienced by infants and children with Pompe disease as a result of voice and swallowing dysfunction. Therefore, there is a need to document the nature of feeding, swallowing, and voice dysfunction experienced by infants and children with Pompe disease, as well the impact of these issues on the quality-of-life in infants and children with Pompe disease. These descriptions will potentially assist healthcare providers in the identification of patients who should undergo further investigation to assess the potential benefits of therapeutic interventions for these problems.

The purpose of this study is to describe the nature of feeding, swallowing and voice dysfunction experienced in a cohort of 15 infants and children with Pompe disease. The secondary purpose of this study is to describe the impact of these issues on the health-related quality-of-life and psychosocial well-being as it pertains to the social, emotional and functional aspects of the child’s life.
CHAPTER II: METHODS

Recruitment/Participants

The study was approved by the Institutional Review Board at Cincinnati Children’s Hospital Medical Center. Potential participants were recruited from the patient population at Cincinnati Children’s Hospital Medical Center in addition to other medical centers providing care for such patients in the United States. A study flyer containing a website link to the internet-based questionnaire was sent to healthcare providers involved in the care of individuals with lysosomal storage diseases. Additionally, a study flyer was sent directly to the parents of patients at Cincinnati Children’s Hospital Medical Center. Information regarding the study was also included in a national Pompe disease support group newsletter to allow for additional recruitment. All interested parents/caregivers were required to access the website link to the internet-based questionnaire in order to participate in the study.

All parents/caregivers of infants and children with a clinical diagnosis of Pompe disease were eligible to participate in the study. Non-English speaking parents/caregivers were ineligible to participate. Implied consent was obtained from all parents/caregivers who completed the voluntary internet-based questionnaire. Parents/caregivers of 19 infants and children previously diagnosed with Pompe disease participated in this study. All participants were from the United States, with the exception of 1 participant from South Africa. The sample population was representative of 9 states across several geographic regions throughout the United States including participants from the Northwest, Southwest, South-Central, Midwest, Mid-Atlantic and Southeast regions. Three individuals from the patient population at Cincinnati Children’s Hospital Medical Center participated in the study. All affected individuals had a
diagnosis of Pompe disease before 6 years of age per parent report. The average age of diagnosis was 1.69 years (± 2.05 SD).

**Instrument**

An investigator-developed internet-based questionnaire was used to examine the severity of feeding, swallowing and voice dysfunction in infants and children with Pompe disease while determining the impact of these issues on the health-related quality-of-life in the study population. The questionnaire was adapted from previously published surveys assessing the severity of feeding, swallowing, and voice dysfunction in other patient populations. These included the Pediatric Voice Handicap Index (pVHI), pediatric voice clinic parent questionnaire, and the Pediatric Assessment Scale for Severe Feeding Problems (PASSFP)[12, 13]. The questionnaire was constructed using a skipped logic format such that parents/caregivers were prompted to answer questions pertinent to the age of their child and was published on the internet via SurveyMonkey®[14].

The Pediatric Voice Handicap Index (pVHI) is a parent-assessment tool used to evaluate the severity of voice disorders in the pediatric population. It consists of 23 statements that provide a numerical score reflective of the severity of voice disorder across the functional, physical and emotional aspects of a child’s life at a cross-sectional time point. Only descriptive analyses were performed in this study, therefore the pVHI was not scored for the purposes of this study.

The pediatric voice clinic parent questionnaire consists of 10 open-ended questions and is used to examine the impact of the child’s voice quality on his or her overall well-being, development, and communication in several areas of the child’s life[12].
The Pediatric Assessment Scale for Severe Feeding Problems (PASSFP) is a tool used to measure the severity of feeding difficulties at a cross-sectional time point. It is a 15-question parent report measure that investigates various aspects of feeding difficulty including: nutritional source, oral sensory, oral motor, behavioral, and quality-of-life concerns[15]. The majority of questions on the PASSFP apply only to individuals who feed orally, even if just a minimal amount. Therefore, results are reported for only those individuals who feed orally (even if minimally). The Pediatric Assessment Scale for Severe Feeding Problems (PASSFP) provides a numerical score reflective of the extent of feeding difficulty; however, the PASSFP was not scored for the purposes of this study as descriptive analyses were used.

Data Analysis

Upon receipt of a completed survey, data was entered into spreadsheets in Microsoft Excel. Descriptive statistics were used in this study given the small number of surveys available for analysis. Frequencies, means, and standard deviations were computed as appropriate.

CHAPTER III: RESULTS

Nineteen parents initiated the internet-based questionnaire. Four of the questionnaires were excluded due to incomplete demographic information. A total of 15 infants and children with Pompe disease were studied. A summary of the demographic characteristics of the infants and children with Pompe disease is presented in Table 1.
Table 1  Demographics of individuals with Pompe disease; N=15

<table>
<thead>
<tr>
<th>Sex</th>
<th>Ethnicity</th>
<th>Primary Form of Feeding</th>
<th>Presence of Tracheostomy Tube and Ventilator Dependence</th>
<th>Mean (±SD) and Age Range of Child at Time of Survey</th>
<th>Mean (±SD) and Age Range of Child at Time of Pompe Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>53% female</td>
<td>73% Caucasian</td>
<td>40% oral feeding</td>
<td>27% yes</td>
<td>6.92 years (±4.63)</td>
<td>1.69 years (±2.05)</td>
</tr>
<tr>
<td>47% male</td>
<td>13% Asian</td>
<td>60% tube feeding</td>
<td>46% no</td>
<td>1.25 years – 16 years</td>
<td>1 month – 5.75 years</td>
</tr>
<tr>
<td></td>
<td>7% African American</td>
<td></td>
<td>27% unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7% Hispanic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oropharyngeal Swallowing Dysfunction

Parents/caregivers who completed PASSFP, reported on children ranging in age from 1.5 years-11 years with a mean age of 5.70 years (±3.10 SD). Of the 15 individuals with Pompe disease who were studied, oral feeding was the primary source of nutrition for 6 individuals while tube feeding was the primary source of nutrition for 9 individuals (Table 1). However, 8 of the 15 individuals were reported to have some degree of oral intake in conjunction with supplemental tube feeding, and therefore were able to complete the PASSFP. Tracheostomy and ventilatory support were not required for 5 of the 8 individuals who were able to complete the PASSFP. Ventilator support and tracheostomy status was unknown in the remaining 3 individuals who completed the PASSFP.

Of those who completed the PASSFP, feeding and swallowing difficulties related to oral-motor skills (strength and range of movements) were commonly noted and were more frequent in children under 6 years. Details of feeding and swallowing difficulties are shown in Table 2.
Approximately 38% of parents/caregivers reported difficulties such as choking, coughing or gagging during oral feeding (n=8). Additionally, 50% of parents/caregivers reported that their children had difficulty with the oral phase of feeding, characterized by prolonged oral holding of foods and liquids with limited active attempts to manipulate the food and/or transfer for swallowing (n=8). Anterior loss of food and liquid was reported as occurring secondary to weakness in lip closure or limitations in tongue movements, or by purposeful anterior propulsion, presumably, reflective of oral feeding resistance. (n=8; 37.5%). Of the children who were reported to receive all of their nutrition from oral feeding, approximately 33% were reported to take longer than 30 minutes to feed (n=6).

Table 2 Swallowing dysfunction resulting from oral motor deficits

<table>
<thead>
<tr>
<th>Subject</th>
<th>Current Age (years)</th>
<th>Age at diagnosis (months)</th>
<th>Tube %</th>
<th>Gag, choke</th>
<th>Holding food/liquid</th>
<th>Anterior Loss</th>
<th>Feed time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 1*</td>
<td>1.42</td>
<td>10</td>
<td>0</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subject 2</td>
<td>2.08</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Subject 3</td>
<td>5.17</td>
<td>7</td>
<td>25</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subject 4*</td>
<td>5.58</td>
<td>30</td>
<td>25</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Subject 5</td>
<td>5.67</td>
<td>42</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Subject 6</td>
<td>7.0</td>
<td>78</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subject 7</td>
<td>7.42</td>
<td>2</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subject 8*</td>
<td>11.25</td>
<td>69</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Tracheostomy and ventilator dependence unknown

Selectivity of certain food textures and/or sensory sensitivity during feeding times was reported by 50% of parents (n=8). Specifically, parents/caregivers reported that their children showed resistance or aversion to warm and/or cold foods. In other cases, parents reported
aversions to particular food textures such as: mixed texture foods, mashed lumpy foods, and hard chewable foods. Of the children with reported food or texture aversions, all were older than 2 years of age. Overall, these clinical signs and symptoms reported, appeared to be related to both oral motor as well as oral sensory factors despite the child’s chronological age.

To assess behavioral factors associated with feeding difficulties, parents/caregivers were asked how willing their child is to accept a spoon, bottle or cup during mealtime. All parents reported that their child always or almost always accept a bottle or cup (n=8). Similarly, almost 86% of parents reported that their child always or almost always displayed anticipatory mouth opening in response to presentation of the spoon (n=7). Anticipatory feeding behaviors were reportedly consistent across this cohort. Overall, few parents/caregivers reported associated behavioral issues impacting feeding success.

Questions regarding feeding-related quality of life were also addressed. When asked if their child enjoys eating, only 50% of parents reported that their child always or almost always enjoys eating (n=8). Moreover, 50% of parents reported feelings of frustration or anxiety when feeding their child (n=8). Collectively, 50% of parents reported that the feeding process has negative impacts on their child or the parent-child relationship during mealtimes.

**Voice Dysfunction**

Responses from the pVHI and pediatric voice clinic parent questionnaire established that the majority of parents/caregivers believe that their child’s voice quality affects their child’s overall well-being and development (n=14; 85.7%). Particularly, parents/caregivers mentioned that their child’s voice may cause frustrations regarding an inability to communicate wants and needs effectively. Parents/caregivers also commented that their children frequently experience
frustration regarding an inability to be understood by others. Some indicated that the frustrations experienced by their child make them less likely to communicate in groups or crowds.

To assess the impact of the child’s voice quality on overall communication, parents/caregivers were asked about the child’s ability to communicate in several different environments. Parents/caregivers reported that their child’s voice affected his or her ability to communicate within the home (n=11; 82%), in social settings (n=12; 92%), and in educational environments (n=10; 90%) (Figure 1). Specifically, parents/caregivers recognized communication difficulties within the home pertaining to difficulties hearing their child call through the house (n=12; 50%). Parents/caregivers frequently reported that their child may become frustrated with his or her inability to be understood by a parent when communicating within the home. Some parents reported that their child expresses more frustrations when he or she is not understood by a parent as opposed to strangers, friends, or other family members. The majority of parents/caregivers reported that people ask their child to repeat him or herself when speaking face-to-face (n=11; 81.8%). Several respondents also indicated that their child may choose to stop communicating if asked to repeat continually by their audience.

Of the parents/caregivers who reported that their child’s voice impacts the ability to communicate in social settings, the most common reason resulted from the child’s speech being difficult for peers to understand (Figure 1). Because the child’s speech may be difficult for others to interpret, parents reported that their child may choose to avoid communication with peers in an effort to avoid having to repeat or allow others to become aware of their speaking difficulties. Almost half of the children were reported to speak less often with friends, neighbors, or relatives because of their vocal quality (n=11, 45.4%). More than 50% of parents reported that their child’s voice difficulties restrict personal, educational and social activities (n=12; Figure 1).
Furthermore, parents/caregivers reported that their child’s voice has impacted their ability to communicate in the educational setting (Figure 1). The most common reason reported was in regard to the low vocal intensity, making it difficult for teachers to hear and understand the child, especially in a noisy environment. Of the parents/caregivers who responded to this question, four reported that their child used alternative methods of communication such as augmentative communication devices or sign language. Despite the impact of voice on the child’s ability to communicate in educational settings, almost 86% of parents/caregivers reported that they are at least somewhat satisfied with support their child receives from his or her school regarding voice and communication (n=7).

A high prevalence of voice-related quality-of-life issues were reported by parents (Figure 1). Parents most commonly reported that their child may become frustrated with his or her voice problem and at least sometimes is annoyed, embarrassed, or frustrated when people ask their child to repeat comments or questions. Only 6 parents reported on whether their child appears tense when talking because of his or her voice; half of whom reported that this problem occurs at least sometimes. Most parents reported that others never or almost never ask about their child’s voice problem (n=11; 81.8%). However, 50% of parents reported that they at least sometimes find that people do not understand their child’s voice problem (n=10). Several parents provided examples of specific concerns their child has expressed about his or her voice. The concerns reported included: being embarrassed about their voice or speech difficulties, becoming frustrated when parents prompt child to cough or swallow in order to be understood, becoming frustrated when asked to repeat several times, avoiding communication with other individuals, and being unwilling to meet new people.
Parents reported issues related to the amount of respiratory effort required for vocalization. When asked to describe the physical effort their child experiences when using his or her voice, parents indicated that their child exerted force to create louder speech, or used extra effort to articulate words requiring complex or rapidly alternating oral motor movements. Other parents reported that their child tired easily when using his or her voice, possibly due to decreased lung capacity and often needed to swallow, or be prompted to cough in order to be understood. When prompted with questions regarding the phonation and resonance of their child’s voice, 80% of parents reported that their child’s voice never or almost never sounds dry, raspy, and/or hoarse (n=10). Seven of thirteen parents described their child’s voice as “soft”, 7 of 13 also reported that their child’s voice sounds “gurgly.” Of the 13 parents who described their child’s voice, 3
indicated that their child’s voice had a hypernasal quality. Vocal intensity overall was described as being consistent throughout the day by the majority of respondents.

CHAPTER IV: DISCUSSION

This aim of this study was to delineate the clinical signs and symptoms of oropharyngeal swallowing and voice dysfunction in infants and children with Pompe disease, while describing the impacts of these issues on the health-related quality-of-life in this population. Previous studies have suggested the presence of oropharyngeal dysphagia and speech disorders in individuals with infantile Pompe disease. The authors of these studies concluded that the prevalence and impact of oropharyngeal dysphagia and speech disorders was significant in their study populations. However, the aforementioned studies used instrumental measure for the physiologic evaluation of speech and swallowing disorders which does not provide information regarding the impact on a child’s quality-of-life. Additionally, characterizations of the clinical signs and symptoms associated with oropharyngeal swallowing and voice dysfunction in individuals with Pompe disease is limited [11, 16]. Collectively, these aspects of swallowing and voice dysfunction are important for overall assessments of health-related quality-of-life and management of these issues in infants and children with Pompe disease.

Oropharyngeal swallowing dysfunction may result in a variety of poor health outcomes including severe respiratory complications, secondary to aspiration, and inadequate caloric intake leading to weight loss and the breakdown of muscle protein [2, 17, 18]. In this study, parental/caregiver reports indicate prolonged feeding times, stress and anxiety present at mealtimes, need for texture alterations, the presence of residue in the oral cavity and pharynx,
and the occurrence of choking, coughing or gagging during oral feeding. Difficulties in the oral and pharyngeal phase of swallow were the most frequently reported problems in our cohort suggesting the need for clinical feeding/swallowing evaluations to identify patients at risk for oropharyngeal swallowing disorders [19]. Clinical signs and symptoms such as choking, coughing or gagging during oral feeding suggest the potential for aspiration resulting from poor coordination of the swallow with airway closure[18, 20], which has significant implications in regard to respiratory health. This is of great concern given the primary cause of death for infants and children with Pompe disease results from cardiorespiratory complications [4]. Despite expectations for the acceptance of various food textures based on the chronologic age of the children in our cohort, aversions to certain hard chewable foods as well as to other specific textures were reported[18]. Food or texture aversions may occur as a result of physiologic problems affecting the airway or gastrointestinal system, sensorimotor insufficiency, or because of behavioral factors influencing feeding[19]. However, behavioral challenges related to the overall willingness to orally feed were not commonly reported. Collectively, this data suggests that feeding difficulties related to food and texture selectivity and prolonged feeding times are most likely the result of physiologically based problems, sensorimotor problems or a combination thereof [17, 18, 21].

The presence of oropharyngeal swallowing dysfunction may significantly impact the health outcomes and quality-of-life in infants and children with these disorders [22]. Therefore, early diagnosis of feeding and swallowing dysfunction may be important in limiting the negative impact on infants and children with Pompe disease. Better understanding of the specific feeding and swallowing problems in individuals with Pompe disease would be beneficial for healthcare providers in the identification of at-risk patients for further investigation with instrumental
measure. Diagnosing a feeding or swallowing disorder requires supportive evidence from both clinical and instrumental evaluation of swallowing to include videofluoroscopic swallow evaluation (VFSE) and/or fiberoptic endoscopic evaluation of swallowing (FEES)[19]. Referrals for these evaluations may be reasonable considering the prevalence of parent reported signs and symptoms suggestive of oropharyngeal swallowing dysfunction and possible compromise in airway protection during swallowing identified in this study.

In addition to affecting the health outcomes of children, feeding and swallowing disorders also impact the quality of life of these individuals and their families. Feeding and swallowing difficulties have been shown to have significant impacts on the parent-child relationship potentially leading to increased parent/caregiver stress[23]. Parent/caregiver reports of prolonged feeding times and increased levels of parent/caregiver stress and anxiety at mealtimes in our study, illustrate that the feeding and swallowing difficulties experienced by this population may be negatively impacting the well-being of children and their parents/caregivers. There is limited research describing the impact of feeding and swallowing dysfunction on children and their families and has been limited to research in specific patient populations. However, healthcare providers who treat infants and children with Pompe disease would not only benefit from a screening tool to identify patients at-risk for oropharyngeal dysfunction, but a tool that also allows for the assessment of feeding-related quality of life issues in this population. It is important for healthcare providers to be aware of the feeding-related quality of life issues affecting both patients and their caregivers in order to provide the most appropriate plan for management of these disorders[24].

The effects on overall health-related quality-of-life and well-being appear to be predominantly due to the negative impact of voice dysfunction as indicated by parent reports on
the pVHI and pediatric voice clinic parent questionnaire. This was evidenced by a high prevalence of parent reports regarding the impact of voice dysfunction on the child’s overall ability to communicate within the home, in social settings and in the educational environment. It is important to consider that although the effects of voice dysfunction primarily impact the individual with Pompe disease, the significant burden of disease on the family is not negligible. Although not a major focus of this study, evidence of parental frustrations or anxiety during feeding times and in communication within the home was identified. This is important information for healthcare providers to consider in the overall assessments of health-related quality-of-life and while making treatment recommendations for this population.

Individuals reported to have a “gurgly” vocal quality may be at risk for aspiration events as this finding suggests the presence of pooled secretions on the vocal cords or the presence of pharyngeal residue of food suggesting the potential for swallowing dysfunction [25]. Additionally, parent reports indicate that the impact of respiratory effort required for vocalization is considerable in our cohort. More than 50% of parents described their child’s voice as being “soft” and described that their child may require extensive physical effort when using his or her voice due to decreased lung capacity. This confirms what is known about the impaired pulmonary function and respiratory insufficiency in individuals with Pompe disease [2, 26]. Given the severity of voice dysfunction reported in this population across the physical, emotional, and functional aspects of the child’s life, it is reasonable to consider routine referral for formal speech-language assessments including voice analysis. If not properly managed, these issues may lead to poorer health outcomes and negative impacts on voice-related quality of life as a result of the inability to communicate effectively in daily life activities.
It is unclear as to which factors have the greatest impact on the development of feeding, swallowing, and voice dysfunction in this population. It is also unclear which factors best predict the feeding, swallowing and voice outcomes in patients with Pompe disease. For that reason, additional research regarding the pathophysiology of oral pharyngeal swallowing and voice dysfunction would be beneficial. Delineation of the motor neuron and muscle involvement as it relates to speech and swallowing dysfunction may be an important avenue for future research as many of the problems reported in this study may be primarily motor in nature. The storage of glycogen in the central and peripheral nervous system of individuals with Pompe disease has been well established [27-29], possibly explaining the features of poor motor function observed in this population[30]. Additionally, studies in mice have shown that effects of respiratory dysfunction may be associated with neuronal involvement [31]. Research has shown that patients with other neuromuscular disorders similarly affecting lower motor neurons, such as Spinal muscular atrophy type II (SMA type II), demonstrate similar swallowing difficulties to those reported in our study population [21]. Patient’s with SMA type II were found to have problems with limited mouth opening in the oral phase, choking on foods and liquids and chewing difficulties possibly related to decreased strength of the masticatory muscles[21, 32]. The signs and symptoms of oropharyngeal swallowing dysfunction observed in patients with SMA type II suggest that oral motor deficits are responsible for some of these feeding difficulties. Therefore, additional investigations regarding the effect of ERT on motor neurons would be useful in determining the mechanism by which swallowing and voice problems occur in individuals with Pompe disease. Further investigation to delineate the exact nature of these issues would be advantageous in order to improve the treatment and management of these issues in infants and children with Pompe disease.
Pompe disease can be considered a continuum of disease with variable severity between the different classifications of the infantile and childhood/juvenile forms [1, 4, 5]. Therefore, parent reports of feeding, swallowing and voice difficulties might be expected to differ between the different classifications of disease and even among patients within the same disease subtype. Certain factors may affect the severity of feeding, swallowing and voice dysfunction including, but not limited to: age of diagnosis, age of first treatment with ERT, the presence of a tracheostomy tube and ventilator dependence, extent of organ involvement, degree of myopathy and the history of speech and/or occupational therapy. Study design and sample size limitations prevented us from taking these factors into consideration collectively; however, we were still able to establish the significant impacts of oropharyngeal swallowing and voice dysfunction in our cohort.

A larger cohort of individuals with Pompe disease might have allowed for more extensive investigation of the clinical characteristics of feeding, swallowing, and voice dysfunction which may be present. Recruitment for studies regarding Pompe disease remains a problem because it is a rare condition. An internet-based questionnaire may not be the most efficient method to assess the feeding, swallowing, and voice difficulties experienced by this population. Given the heterogeneous phenotypes associated with Pompe disease, an individual parent interview may be the most advantageous means of eliciting information regarding the feeding, swallowing and voice difficulties experienced by this population. Specifically, the skipped logic format of this questionnaire may have been confusing for some parents/caregivers and therefore may have contributed to the low response rate for many of the qualitative questions providing the most insight into the impact of oropharyngeal swallowing and voice dysfunction in our study population. Additionally, it is likely that through the recruitment process, this study attracted
highly motivated parents/caregivers and/or parents/caregivers with concerns regarding their child’s feeding, swallowing and voice impairment which may have resulted in selection bias. Nevertheless, the sample size and prevalence of feeding, swallowing, and voice difficulties is similar to those reported in other studies of individuals with Pompe disease [10, 11].

The inherent limitations present when using a parent questionnaire include reliance on parental knowledge and accurate reporting of the child’s feeding, swallowing and voice difficulties. Consequently, there is a possibility of reporting errors. However, this was a cross-sectional questionnaire which minimizes the potential for recall bias. Certainly, in the future, it would be beneficial to conduct prospective studies regarding the nature of feeding, swallowing and voice dysfunction in individuals with Pompe disease. Obtaining qualitative data regarding the feeding, swallowing, and voice difficulties and the associated health-related quality-of-life issues from parents/caregivers participating in focus groups may be an advantageous method for future research.

In conclusion, oropharyngeal swallowing and voice dysfunction were found to have major impacts on the health outcome and health-related quality-of-life in infants and children with Pompe disease. The most common problems contributing to the negative impact on health/well-being included oral phase feeding dysfunction, coughing or choking during oral intake, and reduced ability to communicate with others effectively during daily living activities. This study raises several points regarding the importance of recognizing the characteristics of oropharyngeal swallowing and voice dysfunction. Healthcare providers should be made aware of the high prevalence of these problems in infants and children with Pompe disease in order to identify at-risk patients, initiate therapeutic interventions and make proper management recommendations. At present, routine clinical and/or instrumental evaluation of swallowing may be reasonable for
infants and children with Pompe disease. Additionally, routine referrals for formal speech-language assessments may also be beneficial. This study suggests the need for more stringent standards of care regarding the identification and management of feeding, swallowing, and voice disorders in infants and children with Pompe disease.
REFERENCES


14. SurveyMonkey.com, LLC, Palo Alto, CA, USA


APPENDIX A: PARENT QUESTIONNAIRE

**Questions assessing voice function**

(0= Never 1=Almost Never 2=Sometimes 3=Almost Always 4=Always)

**12 months of age and up**

1. Do you feel like your child's voice has an impact on his/her general well-being and development? If yes, how[12]?

2. My child’s voice makes it difficult for people to hear him/her (0-4)[12]

3. People have difficulty understanding my child in a noisy room (0-4) [12]

4. At home, we have difficulty hearing my child when he/she calls through the house (0-4) [12]

5. My child tends to avoid communicating because of his/her voice (0-4) [12]

6. My child speaks with friends, neighbors, or relatives less often because of his/her voice (0-4) [12]

7. People ask my child to repeat him/herself when speaking face-to-face (0-4) [12]

8. My child’s voice difficulties restrict personal, educational and social activities (0-4) [12]

9. My child runs out of air when talking (0-4) [12]

10. The sound of my child’s voice changes throughout the day (0-4) [12]

11. Please describe your child's voice(e.g. soft, gurgly, hoarse)[12]:

12. Please describe the physical effort (e.g. gets tired, strains) your child experiences when using his/her voice[12]:

**18 months of age and up**

1. Please describe how your child's voice effects his/her overall ability to communicate within the home[12]:

2. Please describe how your child's voice effects his/her ability to communicate in social situations (play, recess, with friends)[12]:

3. People ask, “What’s wrong with your child’s voice?” (0-4) [12]

4. My child’s voice sounds dry, raspy, and/or hoarse (0-4) [12]

5. My child uses a great deal of effort to speak (e.g., straining) (0-4) [12]
6. I find other people don’t understand my child’s voice problem (0-4) [12]

7. In general, how would you say your child’s speaking voice is [33]?
   - excellent
   - good
   - adequate
   - poor or inadequate
   - my child has no voice

8. To what extent does your child’s voice limit his or her ability to be understood in a noisy area [33]?
   ___(A) limited a lot
   ___(B) limited a little
   ___(C) not limited at all

9. My child’s voice is worse in the evening (0-4) [12]

10. My child’s voice “gives out” when speaking (0-4) [12]

11. The quality of my child’s voice is unpredictable (0-4) [12]

12. Do you find your child “straining” when he or she speaks because of his or her voice problem [33]?
   - not at all
   - a little bit
   - moderately
   - quite a bit
   - extremely

13. My child has to yell in order for others to hear him/her (0-4) [12]

3 years of age and up

1. Please describe how your child's voice affects his/her ability to communicate in educational settings[12]:

2. Are you satisfied with the support your child receives from his/her school regarding voice and communication[12]?

3. During the past 2 weeks, to what extent has your child’s voice interfered with his or her normal social activities or with his or her school [33]?
   - not at all
   - good
   - slightly
4. My child appears tense when talking to others because of his or her voice (0-4) [12]
5. My child is frustrated with his/her voice problem (0-4) [12]
6. My child is less outgoing because of his/her voice problem (0-4) [12]
7. My child is annoyed when people ask him/her to repeat (0-4) [12]
8. My child is embarrassed when people ask him/her to repeat (0-4) [12]
9. People seem irritated with my child’s voice (0-4) [12]

4 years of age and up

1. Please describe any concerns your child has about his/her voice (e.g. sometimes embarrassed, sometimes avoids communication, never has a concern) [12]

Questions assessing feeding

All ages

1. Which description best describes your child’s feeding [13]? (please check one)
   ___ (0) It is not safe for my child to feed orally or my child is not able/willing to feed orally so all of my child’s nutrition comes through tube feeding.
   ___ (1) My child is allowed to do some feeding orally, but modifications are required (one certain textures, or fed in a certain position or with certain specific utensils) and the majority of nutrition comes through tube feeding.
   ___ (2) My child is allowed to feed orally and no special modifications are necessary; however, the majority of nutrition still comes through tube feeding.
   ___ (3) My child is allowed to feed orally. Modifications (only certain textures, or fed in a certain position or with certain specific utensils) may or may not be required. The majority of nutrition comes from the oral eating, but some tube feeding is still required.
   ___ (4) My child feeds orally, but special modifications are required. My child does not require any supplemental tube feeding.
   ___ (5) My child feeds orally and no special modifications are required. My child does not require any supplemental tube feeding.
2. Which best describes the way your child receives nutrition [13]? (please check one)

<table>
<thead>
<tr>
<th>ORAL</th>
<th>TUBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

3. My child gags and/or vomits during or just after feeding (either oral or tube): (circle on number on the scale)[13]
Always sometimes never
0--------1--------2--------3--------4

4. My child takes longer than 30 minutes to feed orally: (circle one number on the scale)[13]
Always sometimes never
0--------1--------2--------3--------4

5. My child chokes, coughs or gags during oral feeding: (circle one number on the scale)[13]
Always sometimes never
0--------1--------2--------3--------4

6. My child will open his/her mouth willingly to accept a bottle or cup: (circle one number on the scale)[13]
Always sometimes never
0--------1--------2--------3--------4

7. My child lets food or liquid sit in his/her mouth and does not swallow it: (circle one number on the scale)[13]
Always sometimes never
0--------1--------2--------3--------4

8. My child loses food or liquid out of the mouth—either by letting it drop out or pushing/spitting it out: (circle one number on the scale)[13]
Always sometimes never
0--------1--------2--------3--------4

9. My child enjoys eating: (circle one number on the scale)[13]
Always sometimes never
0--------1--------2--------3--------4

10. I get frustrated or anxious when feeding my child: (circle one number on the scale)[13]
Always sometimes never
0--------1--------2--------3--------4
12 months-3 years of age

1. My child will open his/her mouth willingly to accept the spoon: (circle one number on the scale)[13]
Always sometimes never
0----------1---------2---------3---------4

2. My child whines or cries at feeding times: (circle one number on the scale)[13]
Always sometimes never
0----------1---------2---------3---------4

12 month of age and up

1. Check all the foods that your child will accept and swallow without difficulty [13]:
___ cold foods
___ room temperature foods
___ warm foods
___ liquids
___ pureed foods
___ mixed textures (e.g. soups with chucks of meat or vegetables)
___ mashed lumpy food (e.g. mashed potatoes or mashed vegetables)
___ soft chewable foods (e.g. cookies, crackers, potato chips)
___ hard chewable foods (e.g. meats apples)

Questions assessing receptive and expressive language [34]

EXPRESSIVE LANGUAGE (Yes/No)

0-6 months of age

1. Does your baby cry a lot and in a loud, clear voice?

2. When someone plays with your baby, such as tickling, does she or he laugh and make other happy sounds?

3. Do your baby’s sounds vary from loud to soft and from high to low?

4. Does your baby made sounds such as “pah,” “bah,” or “mah”?

7-12 months of age
1. Does your baby make combinations of sounds such as “pa-dah,” “tah-koo,” “oo-bah,” or “bah-dah”?

2. Even if your baby doesn’t use real words, does she or he sometimes seem to talk in complete sentences or phrases?

13-18 months of age

1. Besides Mama or Dada, does your toddler say some works in the same way each time, so that most people who hear her or him understand what those words mean?

2. Can you tell from the way your toddler’s voice sounds that she or he is asking a questions?

3. When your toddler talks with someone, does she or he often use real words along with motions or gestures?

19-24 months of age

1. Do you believe that your toddler says about 50 words?

2. Have your heard your toddler use any two word sentences or phrases, such as “Throw ball” or “Daddy gone?”

25-36 months of age

1. Does your child say at least two new words each week?

2. When your child can’t make people understand what she or he is saying, does she or he show signs of frustration?

3. When your child says words that have definite beginning and ending sounds, does she or he pronounce both the beginning and ending sounds? Examples: both the /k/ and the /t/ sounds in cat, or both the /j/ and the /s/ in juice

4. Do most people understand what your child is saying most of the time?

5. Does your child use different voice tones and words such as please when speaking to people of different status, such as talking with another child versus talking with a grandparent?
RECEPTIVE LANGUAGE (Yes/No)

0-6 months of age
1. When your baby hears new sounds or voices, does she or he often look toward those sounds?
2. Does your baby now usually stop crying when she or he hears a comforting, sympathetic voice talking to her or him?

7-12 months of age
3. Will your baby sit still and listen for a full minute to a person who is showing and naming pictures of familiar things?
4. Does your baby sometimes obey when you give a simple order such as “Put that down!” or “Come here!”?
5. When someone asks simple “where” questions, such as, “Where is Daddy?” or “Where is the ball?”, does your baby act as if she or he understands what was asked?
6. When your baby hears music with a beat, does she or he try to move to the music’s beat?

13-18 months of age
1. When someone talks to your toddler, even for a long time, does your toddler listen and seem interested?
2. When someone asks your toddler to say words we associate with social routines, such as, “Say ‘Bye-bye’!” or “Can you say ‘Hi’ to Grandpa?”, does your toddler comply?
3. Does your toddler appear to understand new words each week?

19-24 months of age
1. When someone asks your toddler to name things such as animals, toys, or things to wear, does she or he tell you specific examples?

25-36 months of age
1. Do you notice that every day your child seems to recognize the meanings of more and more new words?

2. When asked to pick out one object from a group of five different objects, such as a ball, a book, a crayon, a teddy bear, and a penny, does your child pick the right one?

3. Does your child understand position words? For example, when you talk about an object or person being “behind the door,” or “on top of the table”?

4. Does your child remember the events and sequences of favorite stories so that she or he is able to anticipate what will happen next?