

RUNNING TITLE: LINGUAL STRENGTH IN LOPD

Quantitative assessment of lingual strength in late-onset Pompe disease

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ABSTRACT

Introduction: Skeletal muscle disease resulting in weakness is common in late-onset Pompe disease (LOPD). Recent data implicate common bulbar muscle involvement (i.e., the tongue).

Methods: We used quantitative assessment of lingual strength to determine retrospectively the frequency and severity of lingual weakness in LOPD. We additionally examined associations between lingual strength and the presence or absence of dysarthria, and dysarthria severity.

Results: Quantitative assessment revealed lingual weakness to be present in 80% of the sample. In the 24 affected patients, severity was mild in 29%, moderate in 29%, and severe in 42%. Patients with clinical dysarthria had greater lingual weakness than those without. As dysarthria severity increased, lingual strength decreased by an average of 6.82 kPa.

Discussion: These quantitative data provide additional support for presence of bulbar muscle disease in patients with LOPD. Further study is necessary to determine functional effects, temporal progression, and effects of treatment.

Key words (MeSH): glycogen storage disease type II; Pompe disease; adult glycogen storage disease type II; tongue; muscle weakness; transducer, pressure: quantitative muscle testing

INTRODUCTION

Pompe disease (acid maltase deficiency or glycogen storage disease type II, PD) is an autosomal recessive progressive muscle disease. Muscle weakness results from deficiency of the lysosomal enzyme acid alpha glucosidase (GAA). Prominent skeletal muscle weakness in the extremities and respiratory mechanism is common. The disease is a single condition that manifests clinically across a broad spectrum based on age of onset, rate of progression, and disease distribution. In late-onset Pompe disease (LOPD), disease signs and symptoms principally result from progressive skeletal muscle involvement causing weakness in the lower limbs, trunk, and respiratory muscles¹. The introduction of enzyme replacement therapy (ERT) via infusion of alglucosidase alfa (Lumizyme™) has led to improvements in motor function and stabilization of respiratory function in patients with LOPD^{2,3}.

Although skeletal muscle involvement predominates in LOPD, accumulating data suggest that the bulbar musculature, particularly the tongue muscles, may also be affected. Macroglossia appears to be relatively commonly in infants and children with infantile-onset PD⁴. Case studies provide the earliest suggestion of lingual weakness, as well as dysarthria, in patients with LOPD⁵⁻⁸. More recently, whole-body muscle MRI revealed marked involvement of the lingual musculature in 20 patients with LOPD⁹. We previously described lingual manual muscle testing to assess tongue strength in 19 consecutive patients with LOPD. Lingual weakness ranging in severity was present in 100% of the sample. In the 37% of participants with moderate or severe lingual weakness, dysarthria and/or dysphagia were also present¹⁰.

Although manual muscle testing is a well-accepted technique to assess muscle strength, it is nevertheless a subjective technique dependent on variables such as the skill of the examiner. We now routinely use quantitative muscle testing to measure

lingual strength and identify disease distribution. Quantitative muscle testing (QMT) offers many advantages over manual muscle testing, including the acquisition of precise, reliable interval data that are sensitive to small changes across the entire range of measurement^{11,12}. Quantitative approaches such as muscle dynamometry are particularly useful when normal reference values are available, as is the case for lingual QMT. The use of the Iowa Oral Pressure Instrument (IOPI) for lingual QMT has been validated in a number of studies in both healthy and diseased populations¹³, including some neuromuscular disease populations such as oculopharyngeal muscular dystrophy¹⁴ and amyotrophic lateral sclerosis¹⁵.

We present data on the results of quantitative assessment of lingual strength in a sample of patients with LOPD. We hypothesized that lingual weakness ranging from mild to severe would be common and that tongue weakness would be more severe in those with dysarthria than those without. Additionally, we expected that severity of dysarthria would increase as lingual strength declined.

METHODS

The Duke University Institutional Review Board approved this retrospective research. We reviewed the medical records of all patients diagnosed with LOPD who participated in lingual QMT over a 3-year period at a single academic healthcare center. At our center, patients with LOPD are referred routinely to speech-language pathology for motor speech examination to assess for dysarthria. Quantitative assessment of lingual strength is also completed at this time using commercially available equipment [Iowa Oral Performance Instrument (IOPI); Redmond, WA]. Tongue strength was measured using the methods described in the device manual, including the use of verbal encouragement, at least 3 repeated trials, and rest periods of 30-60 seconds. Mean maximal lingual pressure over 3 trials was obtained in

kilopascals (kPa) and compared to published reference values^{16,17}. When lingual strength was below the 5% lower limit of normal, severity was determined as mild, moderate, or severe based on the values in **Table 1**. A single, licensed speech-language pathologist completed all lingual strength testing.

This clinician also performed a motor speech examination via auditory-perceptual methods to determine the presence of dysarthria and, if present, estimate its severity as slight, mild, moderate, or severe. Severity judgments were made within the framework provided by the World Health Organization's International Classification of Functioning, Disability, and Health model. The ICF qualifies the degree of disability in terms of the degree of activity limitation and participation restriction that results. Accordingly, slight dysarthria, detectable only during isolated speech testing and not present in connected speech, does not result in activity limitation and participation restriction.^{18,19} Terminology from the ICF was used to operationalize the definitions of mild, moderate, and severe dysarthria. Specifically, in terms of influence on activity limitations and participation restrictions, the effects of mild dysarthria were "slight or low", moderate dysarthria "medium or fair", and severe dysarthria "high or extreme".²⁰

Data are presented as mean \pm SD. To determine the relationships between measures of lingual strength in patients with intact speech versus those with dysarthria, we conducted 2-sided *t*-tests and Wilcoxon rank-sum tests. Due to similarities in obtained *P*-values, we present data from the *t*-tests for simplicity in interpretation. To determine the relationships between lingual strength and ordinal classification of dysarthria severity, regression analyses were conducted. Statistical significance was set at the 0.05 level for all analyses.

RESULTS

Thirty patients with late-onset Pompe disease completed lingual QMT over a 3-year period from 2009 to 2012. Individual patient demographic and raw data are provided in **Table 2**. The sample was comprised of 22 women (70%) and 8 men (30%) with a mean age of 51 ± 13.9 years. Twenty-eight patients were Caucasian (93%), and 2 patients were Hispanic (7%). Thirteen participants ambulated independently (43%), 15 ambulated with assistance (50%), and 2 were wheelchair dependent for mobility (7%). At the time of lingual QMT, 8 patients were not on ERT (27%), 4 had been on ERT for < 1 year (13%), 4 had been receiving ERT for 1 to 3 years (13%), and 14 had been on ERT for > 3 years (47%).

Across all 30 patients, mean maximum lingual pressure was 29.2 ± 12.95 kPa [median = 29.5; range: 51 (8-59)]. Lingual weakness was present in 80% of patients. In patients with lingual weakness, severity was mild in 29% (n=7), moderate in 29% (n=7), and severe in 42% (n=10).

These 30 patients all also participated in a motor speech examination. Overall, 87% of patients (n = 26) were diagnosed with dysarthria, and 13% (n = 4) were diagnosed with intact motor speech function (i.e., no dysarthria detectable). In patients with dysarthria, 23% (n = 6) had slight dysarthria, 54% (n = 14) had mild dysarthria, and 19% (n = 5) had moderate dysarthria. There were no instances of severe dysarthria. Severity was not established in 1 patient (4%) diagnosed with dysarthria.

There was no statistically significant difference ($P = 0.08$) in lingual strength in patients with intact motor speech function (40.25 ± 7.27 kPa) versus those with dysarthria (27.50 ± 12.87 kPa). However, considering that there were only 4 patients without dysarthria, the precision and power of the statistical analyses was limited.

Therefore, we pooled patients with intact motor speech function and those with slight

dysarthria ($n = 10$) and compared them to pooled subjects with mild and moderate dysarthria ($n = 19$). This was justified based on the operational definition of slight dysarthria; that is, speech function was within functional limits in connected speech with deficits only detectable in maximum performance speech tasks. A statistically significant difference was detected ($P = 0.009$) between lingual QMT in the 10 patients with speech that was within functional limits (38.20 ± 8.20 kPa) versus the 19 patients with mild or moderate dysarthria (25.32 ± 13.05 kPa).

A statistically significant difference ($P = 0.007$) was present between lingual strength and dysarthria severity. That is, as dysarthria severity increased, there was an average decline of 6.82 kPa in lingual strength. Mean lingual strength was 40.25 ± 7.27 kPa in patients with intact motor speech function. In patients with dysarthria, mean lingual strength was 36.83 ± 9.15 kPa when severity was slight, 26.50 ± 14.92 kPa when severity was mild, and 22.00 ± 4.90 kPa when severity was moderate.

DISCUSSION

This study provides quantitative data demonstrating lingual weakness in LOPD. Our results suggest that lingual weakness is common in this population and that severity is often marked. In this sample, 57% of all patients had tongue weakness that was moderate or severe. This increased to 71% when we just considered the patients with quantifiable lingual weakness. These data are consistent with prior anecdotal⁵⁻⁷ and experimental^{9,10} observations. Importantly, these results refine understanding of disease distribution and phenotype characteristics in LOPD.

We also found a relationship between lingual strength and dysarthria. There were statistically significant differences in lingual strength in patients with speech that was within functional limits versus those with clinical dysarthria. In patients with

speech that was within functional limits, mean lingual strength was 38.20 kPa versus 25.32 kPa in those with dysarthria. Additionally, as severity of dysarthria increased, mean lingual strength decreased by an average of 6.82 kPa. However, these associations do not imply causality, and additional investigation is required to understand the relationships between dysarthria and lingual weakness in LOPD.

Indeed, even patients without clinical dysarthria demonstrated mild lingual weakness, on average, which suggests other factors besides or in addition to tongue weakness contribute to dysarthria.

The limitations of this exploratory study include use of a convenience sample, its retrospective nature, and the use of an unblinded clinician to measure lingual strength and determine the presence and severity of dysarthria. However, these data provide direction for future study. For example, the relationship, if any, between lingual weakness and the development and progression of dysarthria, as well as oropharyngeal dysphagia, warrant further investigation. Similarly, determination of the relationship between weakness of the bulbar muscles of the tongue and the skeletal muscles of the extremities and respiratory mechanism is warranted.

Moreover, investigation of the effects of ERT on lingual strength (and speech) appears an important target for future research. Such research would optimally include longitudinal data obtained before the initiation of ERT. Longitudinal data will also improve understanding of the onset and progression of lingual weakness and the associated functional effects. Additionally, an important future step in this line of research will be to determine the relationship between lingual strength and anatomy and composition via MRI. Although the dominant abnormality of fatty muscle infiltration can be challenging to quantify technically, our research group has initiated use of a proton density fat fraction technique, previously validated in the liver²¹, in

patients with PD. Such technology will allow acquisition of data that can be used to determine correlations between measures of pathology and measures of body function.

Perhaps most importantly, future research in this area should investigate whether quantitative lingual strength assessment can contribute to the differential diagnosis of LOPD and perhaps other neuromuscular disorders such as the muscular dystrophies. The diagnosis of LOPD is often delayed considerably following initial medical presentation due to diagnostic challenges such as the heterogeneity in clinical presentation and disease signs and symptoms which overlap with other conditions. However, tongue weakness that can be appreciated upon careful examination may be present early in the disease course, even in patients who are asymptomatic¹⁰. Further investigation may demonstrate that the finding of lingual weakness may increase the suspicion for LOPD. Early diagnosis in LOPD is important, as it appears that prognosis and response to treatment is dependent largely on early initiation of ERT. Therefore, efforts to improve differential diagnosis remain paramount for future research.

ABBREVIATIONS

ERT: enzyme replacement therapy

GAA: acid alpha glucosidase

ICF: International Classification of Functioning, Disability, and Health

LOPD: late-onset Pompe disease

PD: Pompe disease

QMT: quantitative muscle testing

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DISCLOSURES

HNJ has received research/grant support and honoraria from Genzyme Corporation.

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TABLES

Table 1. IOPI Norms and Interpretation Values

Age (years)	Normal Strength (kPa)	5% LLN	Mild Weakness (kPa)	Moderate Weakness (kPa)	Severe Weakness (kPa)
Young (20 to 39)	66 (13.0)	44	44-34	33-23	≤22
Middle (40 to 60)	63 (12.2)	43	43-33	32-22	≤21
Older (60+)	57 (13.0)	37	37-29	28-20	≤19

Norms for adults stratified by age (IOPI 2.2 manual) and the guidelines used for interpretation of abnormal values by severity used in this study.

Table 2. Subject demographic and raw data

Subject	Gender	Age	Ethnicity	ERT Status	Ambulatory Status	Lingual Strength (kPA)	Lingual Weakness (Severity)	Dysarthria Severity
1	W	45	C	> 3 years	Ambulatory with assistance	59	WNL	Mild
2	M	55	C	> 3 years	Ambulatory with assistance	27	Moderate	Moderate
3	W	39	C	1-3 years	Ambulatory with assistance	38	Mild	Slight
4	W	58	C	> 3 years	Ambulatory with assistance	32	Moderate	Mild
5	W	45	C	No ERT	Ambulatory	35	Moderate	Slight
6	W	46	C	> 3 years	Ambulatory	26	Moderate	Mild
7	W	72	C	> 3 years	Ambulatory with assistance	17	Severe	Mild
8	M	60	C	No ERT	Ambulatory	32	Mild	Mild
9	W	68	C	No ERT	Ambulatory with assistance	51	WNL	WNL
10	W	64	C	1-3 years	Ambulatory with assistance	8	Severe	Mild
11	M	43	H	> 3 years	Ambulatory	16	Severe	Mild
12	W	29	C	No ERT	Ambulatory with assistance	50	WNL	Slight
13	M	54	C	< 1 year	Ambulatory with assistance	15	Severe	Moderate
14	M	65	C	No ERT	Ambulatory with assistance	43	WNL	Mild
15	M	54	C	> 3 years	Ambulatory with assistance	24	Moderate	Moderate
16	W	51	C	> 3 years	Ambulatory with assistance	13	Severe	Mild
17	W	54	C	No ERT	Wheelchair	19	Severe	Moderate
18	M	47	C	1-3 years	Ambulatory	38	Mild	WNL
19	W	48	C	No ERT	Ambulatory	18	Severe	Mild
20	W	69	C	< 1 year	Wheelchair	13	Severe	-
21	W	8	H	> 3 years	Wheelchair	12	Severe	Mild
22	W	48	C	> 3 years	Ambulatory with assistance	35	Mild	WNL

23	W	24	C	1-3 years	Ambulatory	25	Moderate	Moderate	
24	W	64	C	> 3 years	Ambulatory with assistance	40	WNL	Mild	
25	W	57	C	< 1 year	Ambulatory with assistance	22	Moderate	Slight	
26	W	45	C	> 3 years	Ambulatory	40	Mild	Mild	
27	W	57	C	1-3 years	Ambulatory with assistance	35	Mild	Slight	
28	W	61	C	No ERT	Ambulatory	15	Severe	Mild	
29	W	61	C	> 3 years	Ambulatory	41	WNL	Slight	
30	M	41	C	< 1 year	Ambulatory	37	Mild	WNL	
		W=22 (70%)	X=51 (13.9)	C=28 (97%)	No ERT=8 (27%)	Ambulatory=13 (43%)	X=29.2 (12.95)	WNL=6	WNL=4
		M=8 (30%)		H=2 (3%)	<1 year=4 (13%)	Assistance=15 (50%)		MILD=7	SLIGHT=6
				1-3 years=4 (13%)	Wheelchair=2 (7%)			MODERATE=7	MILD=14
				>3 years=14 (47%)			SEVERE=10	MODERATE=5	

Subject demographic and raw data including gender (W=women, M=men), age, ethnicity (C=Caucasian, H=Hispanic), ERT status, ambulatory status, lingual strength, severity of lingual weakness, and severity of dysarthria (X=mean).