EXPANDING THE PHENOTYPE OF LATE-ONSET POMPE DISEASE: TONGUE WEAKNESS: A NEW CLINICAL OBSERVATION

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ABSTRACT: *Introduction*: Following the clinical observation of lingual weakness in 2 patients with late-onset Pompe disease (LOPD), tongue strength was assessed in 19 consecutive patients to determine the frequency and severity of this neurological sign. *Methods:* Lingual strength was assessed using manual muscle testing; if weakness was present, severity was established as mild, moderate, or severe. *Results:* All the patients exhibited lingual weakness, even 2 asymptomatic patients with a positive family history. Weakness was mild in 12 (63%), moderate in 6 (32%), and severe in 1 (5%). Dysarthria and/or dysphagia were observed or reported in 7 of 19 (37%) patients. *Conclusions:* Lingual weakness may be present as an axial sign of LOPD, even relatively early in the disease course, and may contribute to the differential diagnosis of this now treatable condition. Dysphagia and/or dysarthria may also occur. This finding further expands the phenotype of LOPD.

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Pompe disease (i.e., glycogen-storage disease type II) is a rare autosomal recessive neuromuscular disease that occurs in 1 of 40,000 births due to a deficiency of the lysosomal enzyme acid α-glucosidase (GAA).[1] Although the most severe phenotype of Pompe, the infantile form, results from a complete lack of GAA, patients with incomplete GAA deficiency may present later in childhood, adolescence, or adulthood [late-onset Pompe disease (LOPD)]. Patients generally report symptoms primarily related to skeletal and respiratory muscle involvement, such as slowly progressive lower limb weakness, respiratory fatigue, and dyspnea. There is marked heterogeneity in the severity and progression of the disease. Similarly, the age of disease onset varies from the first to sixth decades of life. The signs and symptoms often resemble those of other neuromuscular diseases, resulting in delayed diagnosis. Patients commonly describe a several-year history of changes in gait, respiratory function, sleep, endurance, and/or exercise/activity tolerance prior to diagnosis.[2–4]

Alglucosidase alfa (Myozyme/Lumizyme) has been approved in the USA and EU as the first treatment for this devastating disease.[5,6] A recent clinical trial using alglucosidase alfa for enzyme replacement therapy (ERT) in individuals with LOPD demonstrated increased walking distance and stabilization of pulmonary function over 18 months.[7] With the introduction of ERT, early diagnosis has become increasingly important, as improved prognosis appears to be associated with early initiation of therapy.[8–10]

ERT with alglucosidase alfa has altered the natural history of LOPD, and the clinical characteristics of the disease are being increasingly characterized. Involvement of the orofacial structures and their striated musculature has received relatively little attention, although pathologic study of a single case revealed damage of every striated muscle examined, including the muscles of the tongue.[11]

Based on the clinical observation of lingual weakness and dysarthria or dysphagia in 2 patients with LOPD, tongue strength was systematically assessed in a series of 19 consecutive patients with confirmed disease at a single academic health-care center in order to determine the frequency and severity of lingual weakness in this population.

METHODS

Following the clinical finding of lingual weakness in 2 LOPD patients with dysphagia or dysarthria, tongue strength was assessed in an additional 17 consecutive patients with confirmed disease from September 2007 to August 2010. Pompe disease was confirmed via enzymatic assay and/or gene mutation analysis in all cases. A standard physical examination was completed, including manual muscle testing (MMT) in 35 muscle groups, pulmonary function testing (e.g., FVC), and functional assessments of gross motor function (e.g., timed tests of stair climbing, arising from the floor, 10-meter ambulation). Lingual MMT was added to this standard protocol. All participants were assessed by the same experienced examiner (A.D.), with over 30 years of experience in the use of

Abbreviations: ERT, enzyme replacement therapy; F, female; FVC, forced vital capacity; GAA, α-glucosidase; IOPI, Iowa Oral Performance Instrument; IV, invasive ventilation; LOPD, late-onset Pompe disease; M, male; MMT, manual muscle testing; MRI, magnetic resonance imaging; NA, not applicable; NIV, non-invasive ventilation; STIR, short-time inversion recovery; TSE, turbo spin–echo

Key words: glycogen-storage disease type II, late-onset Pompe disease, lingual weakness, phenotype, Pompe disease, tongue, tongue weakness

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Table 1. Scale used for determining lingual strength.

Severity	Operational definition	Functional symptoms
Normal lingual strength	The patient is able to push with the tongue against the inside of the cheek, opposing high resistance from the examiner	Asymptomatic
Mild lingual weakness	The patient is able to push with the tongue against the inside of the cheek but can be overcome by high resistance from the examiner	Asymptomatic
Moderate lingual weakness	The patient is unable to completely push with the tongue against the inside of the cheek and can easily be overcome by the high resistance provided by the examiner	Mild dysphagia and/or dysarthria present though often not reported by patients without direct questioning
Severe lingual weakness	The patient is unable to push with the tongue against the inside of the cheek to provide any resistance to the examiner	Overt dysphagia and/or dysarthria

MMT in the examination of neuromuscular diseases. Patients were instructed to push laterally with their tongue against their inner cheek bilaterally. The examiner simultaneously opposed with his opposite thumb and attempted to overcome the patient's lingual force while bracing with the opposite hand on top of the patient's head. In normal healthy individuals, it is generally not possible to overcome lingual resistance with this approach. Lingual strength was assessed to be normal or abnormal; if abnormal, severity of weakness was determined to be mild, moderate, or severe, based on the scale in Table 1. Patients were also asked about any speech and/or swallowing difficulty, and speech was subjectively assessed for evidence of dysarthria. To elicit complaints regarding swallowing, it was generally necessary to inquire specifically about oral stage functioning such as difficulty using the tongue to manipulate the bolus or clear oral residue.

RESULTS

Individual subject demographic information is provided in Table 2. Lingual weakness was present in all 19 subjects, including 2 asymptomatic individuals. Of the 19 patients, lingual weakness was mild in 12 (63%), moderate in 6 (32%), and severe in 1 (5%). Subjects ranged in age from 14 to 78 years (mean 44.15 years, SD 13.59 years). Among the 17 symptomatic patients (89%), the duration of symptoms ranged from 1.5 to 32 years (mean 15.97 years, SD 8.65 years). MMT muscle score ranged from 48 to 342 out of a possible 350 (median = 267), and there were 6 female and 13 male subjects. Twelve participants (63%) received ERT, whereas 7 (37%) did not. There were a variety of reasons the 7 participants were not receiving ERT at the time of lingual strength assessment. In 4 cases, ERT was not thought to be indicated at the time by the treating physician due to mild or absent symptoms. Another participant declined treatment due to advanced age and, in 2 cases, initiation of ERT was delayed due to issues related to medical insurance.

DISCUSSION

We studied lingual strength in 19 consecutive adult patients with confirmed LOPD who were seen at an academic health-care center. In these 19 participants, lingual weakness was found in 100% of the sample, including 2 asymptomatic patients (10 and 11) diagnosed due to a positive family history. Lingual weakness was most commonly mild and therefore less overt than other signs on examination, although in 7 of 19 (37%) participants weakness was at least moderate and, in 1 case, severe. Although reported in children with the infantile form of the condition,[12] macroglossia was not present in any of the participants in this study.

These data suggest lingual weakness occurs relatively early and frequently in individuals with LOPD, a finding that, to our knowledge, has not been reported previously. Although additional study is required, the finding of lingual weakness on examination may be an important observation in the differential diagnosis of late-onset Pompe, which is often challenging and may include multiple forms of muscular dystrophy or other muscle diseases. Although tongue weakness is not a presenting symptom of LOPD, based on these results it may be an important early clinical sign appreciated upon careful examination. This is of particular relevance now that ERT is available, and data show early intervention improves outcomes.[8–10] In addition, patients can develop functional consequences of lingual weakness, such as dysphagia and dysarthria.

Magnetic resonance imaging (MRI) was performed in 1 participant (subject 13, Fig. 1) with moderate lingual weakness. Sagittal T1 and axial T2 turbo spin–echo (TSE) sequences were remarkable for diffuse fatty infiltration and muscle

Table 2. Descriptive data regarding the 19 study participants.

Participant number	Age (y)	Gender	Years since symptom onset	MMT total score*	FVC/% predicted	Respiratory assistance (age of initiation)	Severity of lingual weakness	ERT
1	43	M	10	48	0.96/21	NIV (38)	Mild	Yes
2	41	M	13	272	3.04/67	NIV (35)	Mod	Yes
3	41	M	14	228	2.45/38	NIV (37)	Mod	Yes
4	36	M	14	267	1.23/23	NIV (30)	Mod	Yes
5	14	M	7	242	3.26/73	NIV (440)	Mild	Yes
6	46	M	26	279	2.26/54	NA	Mild	Yes
7	49	F	14	268	1.62/49	NIV (47)	Mild	Yes
8	39	M	26	154	0.61/14	IV (15)	Severe	Yes
9	47	M	8	259	2.58/51	NA	Mild	Yes
10	30	F	NA	325	3.22/76	NA	Mild	No
11	35	M	NA	342	3.89/72	NA	Mild	No
12	78	F	30	235	1.51/67	O_2 conc (69)	Moderate	No
13	62	M	20	276	1.9/39	O_2 conc (93)	Moderate	No
14	49	M	19	252	1.97/34	NA	Mild	Yes
15	47	F	1.5	270	3.02/87	NA	Mild	No
16	29	M	8	267	2.31/40	NIV (29)	Mild	No
17	58	F	10	256	1.63/58	NA	Mod	Yes
18	52	M	32	285	3.8/74	NA	Mild	No
19	42	F	19	275	2.97/89	NA	Mild	Yes

MMT, manual muscle testing; FVC, forced vital capacity; ERT, enzyme replacement therapy; M, male; F, female; NA, not applicable; O_2 conc, oxygen concentration.
**Score out of a maximum of 350 points.*

atrophy. Coronal T2 short-time inversion recovery (STIR) further revealed peripheral venous drainage of the tongue. Although comparative data are limited, Carlier and colleagues[13] recently examined muscle involvement in 20 subjects with LOPD using whole-body MRI: "All facial muscles are spared except for the tongue, in which fatty infiltration was intense and precocious" (p. 23). These findings are consistent with the MRI findings in subject 13 and provide insight into the underlying pathophysiology.

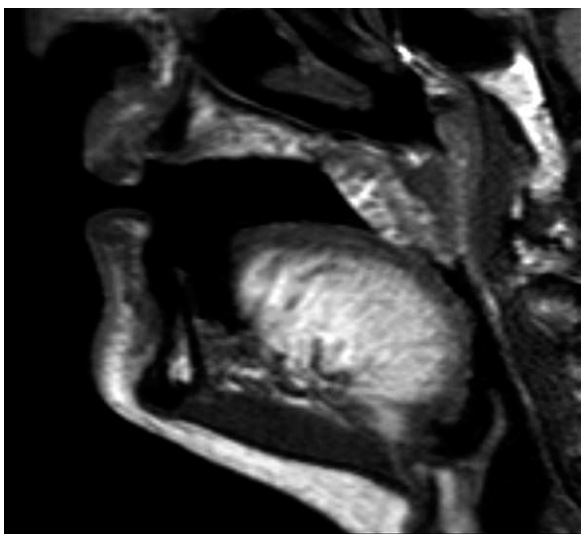

FIGURE 1. MRI performed in subject 13, who had moderate lingual weakness. Imaging reveals diffuse fatty infiltration of the tongue, lingual muscle atrophy, and peripheral venous drainage of the tongue.

This data are preliminary and limited in many respects. Such limitations include the subjective nature of MMT, the small sample size, and the lack of a blinded examiner. In addition, this cross-sectional study was not designed to determine the influence of ERT on lingual strength, which is unknown. Regarding the subjective nature of MMT, it is a well-accepted method for assessing muscle strength in a typical clinical setting and is routinely employed by neurologists, physical therapists, and other health-care professionals.[14] However, quantitative data obtained via use of an instrumental measurement approach would be clearly preferred. Such technology is now readily available commercially [e.g., Iowa Oral Performance Instrument (IOPI); IOPI Northwest Co., Carnation, Washington]. The IOPI employs single-use, air-filled, intraoral tongue bulbs to precisely measure lingual strength in kilopascals. The continuous data obtained may be compared with normative data.[15] At a minimum, measurement of such continuous dependent measures would be statistically more robust than ordinal measures such as MMT. The approach is particularly appealing for use in clinical trials, when detection of change between groups is vital.

Determination of the functional influences of lingual weakness (i.e., speech and swallowing disorders) also requires additional study. It is, for example, possible that more sensitive assessments of speech and swallowing may reveal more subtle functional influences. However, our experience

suggests that both dysphagia and dysarthria may be encountered in this patient population. In this study, upon direct inquiry, one third of patients complained of symptoms of dysphagia, such as impairment in oral bolus control (patients 3, 4, 8, 12, 13, and 17). For example, subject 8, a non-ambulatory 39-year-old man with a 26-year history of symptoms and severe lingual weakness, complained of difficulty swallowing and reported increased coughing during meals. Severe dysarthria was present in subjects 2 and 4 (as well as tongue atrophy in subject 4). Reductions in lingual strength may be underrecognized by patients and, in our experience, direct questioning regarding speech and swallowing were generally necessary to elicit patient complaints. Behavioral interventions to address lingual weakness in LOPD may also be needed. Exercise-based treatments such as lingual resistance training have been demonstrated to enhance tongue strength (as well as aspects of swallow performance in some instances) in a variety of populations, including healthy adults of various ages[16–18] and acute and chronic patients with dysphagia after stroke.[19]

Future studies will continue to define disease distribution in this condition, and lingual weakness may emerge as another axial disease sign and part of the disease distribution. Early involvement of the axial muscles of respiration, including the abdomen, is often reported, as is early compromise of neck strength.[3] In addition, the paraspinal and periscapular muscles are frequently affected.[20] In more select cases, eyelid ptosis responsive to ERT has been described.[21] From this perspective, weakness of the muscles of the tongue may also be considered a possible axial sign of LOPD, and one that may be prone to early effects of the disease.

Based on these findings, we have several recommendations for clinical practice, including that strength testing of the orofacial structures, including the tongue, be performed routinely in the assessment of neuromuscular disorders. Presently, most neuromuscular disease examinations are limited to inspection for fasciculations and atrophy of the tongue and are thus insufficient in this respect. In addition, direct inquiry is recommended regarding changes in speech and swallowing function in patients with known or suspected adult-onset Pompe disease, as initial symptoms may be mild, especially in comparison to their major complaints. Finally, careful lingual MMT is required by clinicians, as weakness in many cases was mild but evident upon careful examination.

In conclusion, lingual weakness was present in 100% of 19 consecutive subjects with LOPD seen over a period of approximately 3 years. Mild lingual weakness was present even in 2 asymptomatic patients, suggesting that weakness in axial tongue muscles may be an early manifestation of the disease. This finding expands the known phenotype of LOPD. Future research is needed to quantify lingual strength in patients with Pompe disease to allow for response to treatment and change over time to be studied most efficiently. The functional influences of lingual weakness also require additional study, as do the effects of ERT on lingual strength. Lingual resistance training may also prove to be an important behavioral intervention to explore in this population, especially as functional consequences emerge and develop. Thus, assessment and measurement of lingual strength may prove useful both clinically and scientifically in LOPD.

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