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Oropharyngeal dysphagia may occur in late-onset Pompe disease, implicating bulbar muscle involvement

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Abstract

Late-onset Pompe disease (presenting after 12 months of age) often presents with limb-girdle and respiratory weakness, but oropharyngeal dysphagia has not been reported previously. A retrospective review of all late-onset Pompe disease patients evaluated in the neuromuscular clinic at Duke University Medical Center from 1999–2010 was performed. Twelve patients were identified and 3 had symptoms of oropharyngeal dysphagia. The medical record was reviewed, including the results of electromyography, videofluroscopic swallow examinations, and motor speech examination including instrumental assessment of lingual force with the Iowa Oral Performance Instrument. Oropharyngeal dysphagia was mild in two cases and severe in one. One of the two patients with mild severity demonstrated oral stage swallow signs; in the other, residual material was observed in the area of the cervical esophagus. In the patient with severe oropharyngeal dysphagia, both the oral and pharyngeal stages of swallowing were affected with penetration and aspiration documented. The degree of swallowing impairment appeared to correlate with overall physical strength and function. Oropharyngeal dysphagia may occur in patients with late-onset Pompe disease, implicating bulbar muscle involvement. Screening for symptoms of dysphagia may help reduce morbidity and mortality, while improving understanding of the late-onset Pompe disease phenotype. Further studies, including examination of the relationship between lingual weakness and oropharyngeal dysphagia, are warranted.
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1. Introduction

Late-onset Pompe disease (LOPD), disease occurs due to partial deficiency of the lysosomal enzyme acid α-glucosidase (GAA) with onset of respiratory insufficiency, fatigue, muscle weakness, and gait changes between juvenilia and middle-age [1–3]. LOPD has received increased attention since the introduction of enzyme replacement therapy (ERT). Treatment benefits have been demonstrated in both the infantile and late-onset forms of the disease [4–8]. With the availability of treatment, increasing emphasis has been placed on diagnosis. Ptosis [9–14], impaired gastric function [15], cardiac involvement [16], smooth muscle disease, and lingual weakness [17] have recently been described. Identification of the complete LOPD phenotype is important in providing comprehensive, interdisciplinary care.

Oropharyngeal dysphagia is not a well-recognized symptom in patients with LOPD, but it is perhaps not surprising considering recent reports of lingual weakness in LOPD [17]. Autopsy reports have also described vacuolar myopathy in the genioglossus and proximal esophagus [18]. We describe three patients with LOPD and symptoms of oropharyngeal dysphagia who received a detailed evaluation.

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2. Methods

The Duke University Institutional Review Board approved this work. Twelve adult patients with LOPD were seen in the neuromuscular clinic for electromyography studies and their records reviewed [19]. Of these, three patients with symptoms of oropharyngeal dysphagia were identified. Primary findings were as follows:

2.1. Patient 1

Patient 1 was a 39–year-old female diagnosed with LOPD at age 37 after two decades of progressive disease signs and symptoms, beginning with elevated transaminases and lower extremity pain. At the time of diagnosis, she required nocturnal BiPAP for obstructive sleep apnea, but denied any difficulties swallowing. Initial physical examination revealed moderate proximal lower extremity weakness. EMG demonstrated complex repetitive and myotonic discharges isolated to the paraspinal muscles. The diagnosis of LOPD was confirmed by analysis of GAA activity and genetic testing. She initiated ERT less than two months later (20 mg/kg every 2 weeks.).

Two years later, she reported the recent onset of swallowing difficulty, describing a globus sensation with solids. There was no recent history of unintended weight loss or pulmonary infection. Physical examination was stable with unchanged lower extremity weakness (2/5 hip flexor weakness, 5/5 strength distally). Upper extremity strength as measured by hand strength dynamometry was slightly improved (27.8–28.9 kg). Her forced vital capacity measures had been stable over the two-year period (44–46% upright, 25–30% supine).

A motor speech examination was performed including tasks of maximum performance, perceptual speech assessment of speech in a variety of tasks, and instrumental assessment of lingual and respiratory force. She was found to have a slight dysarthria, flaccid in nature. Digital pressure gauge manometery was used to obtain mean maximum inspiratory and expiratory pressures (MIP, MEP) over three trials. Mean MIP was 34 cm H20 (sd = 1.5) and mean MEP was 48 cm H20 (sd = 2.6), consistent with moderate inspiratory and expiratory weakness, respectively. Lingual strength was determined using the IOPI to measure lingual force in kilopascals (kPa) over three trials using standard procedures [20]. Mean lingual force was 38 kPa (sd = 0.6), reflecting mild weakness [21]. Results of the 3-oz water test were positive, as she removed the cup from her lips five times and the total duration was extended (25 s) [22]. Finally, the Communicative Effectiveness Survey (CES) was administered [23]. This 1–4 point scale asks patient to rate their communicate effectiveness in a variety of communication situations (e.g., speaking on the phone). The patient indicated very effective communication skills with a total score of 32/32.

A videofluoroscopic swallowing examination (VFSE) demonstrated mild pharyngeal dysphagia. Swallow signs included diminished pharyngeal stripping wave and mild post-swallow pharyngeal residue. Marked post-swallow residue was found in the cervical esophagus. She declined further diagnostic testing for esophageal dysphagia.

2.2. Patient 2

Patient 2 was a 54-year-old male diagnosed with muscle biopsy confirmed LOPD at age 29 after developing progressive dyspnea on exertion. He became unable to ambulate without a walker at age 51 and began using BiPAP while upright to reduce respiratory effort. Around this time, he noted swallowing difficulty and required a pureed diet prior to evaluation at our center. He had difficulty maintaining his weight, but with protein supplementation was able to keep a normal body mass index (BMI) of between 22 and 23.

The patient had received 3 years of ERT (20 mg/kg every 2 weeks) prior to presentation, but had continued to experience slow progression. His physical examination was positive for mild weakness of eye closure and moderate weakness of tongue protrusion via manual muscle strength testing. Dysarthria was present, as was severe proximal weakness in the upper and lower extremities. He had lost 4.5 kg in the 6 months prior to evaluation. EMG demonstrated low amplitude, short duration, polyphasic motor unit potentials in limb muscles with myotonic discharges isolated to the paraspinal muscles. Complex repetitive discharges were present in limb muscles.

Motor speech examination revealed a flaccid, moderate dysarthria, characterized by decreased loudness in connect speech, decreased maximal and range of loudness, the use of short phrases to pause for respiration, and decreased speech intonation and stress. Digital pressure gauge manometery was used to obtain mean MIP and MEP over three trials. Mean MIP was 18 cm H20 (sd = 0.6) and mean MEP was 27 cm H20 (sd = 3.4), consistent with severe inspiratory and expiratory weakness, respectively. Lingual strength was determined as previously described. Mean lingual force was 24 kPa (sd = 1.7), reflecting moderate lingual weakness. The Communicative Effectiveness Survey (CES) was administered and the patient's total score was 22/32, which suggested a functional influence of his dysarthria.

VFSE was performed and he was found to have moderate oropharyngeal dysphagia characterized by the following swallow signs: airway invasion including frequent penetration and occasional aspiration, slowness in anterior–posterior transport of the bolus, and post-swallow oropharyngeal residue. The patient was offered a trial of a behavioral based dysphagia treatment program but he declined due to the distance and was lost to follow-up.

2.3. Patient 3

The patient was a 57-year-old female who noted onset of mild lower extremity weakness at age 53. She developed

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difficulties ascending stairs and arising from a seated position. She was diagnosed with LOPD by muscle biopsy and genetic testing by muscle biopsy, beginning ERT at 20 mg/kg every 2 weeks shortly after diagnosis.

Approximately four years later, the patient reported that "sometimes it feels like my tongue is not working like it should." She denied any difficulty swallowing food, but noted some difficulty with pill swallowing that was improved by dipping the pill in olive oil prior to swallowing. Her weight was stable with a BMI of 19.8. Physical examination was notable for mild lingual weakness, as well as stable mild proximal upper and stable severe lower extremity weakness (2/5 hip flexor weakness). Handgrip dynamometry measurements were stable, but her 6 min timed walk distance had improved from 132 to 357 m. FVC measurements remained in the 70% range when upright and 56–62% supine. An EMG examination demonstrated scattered myopathic motor unit potentials in extremity muscles with spontaneous activity (i.e. fibrillations, positive sharp waves, complex repetitive discharges, myotonic discharges) isolated to the paraspinal muscles.

Motor speech examination revealed dysarthria only under maximum performance speech conditions. Digital pressure gauge manometery was used to obtain mean MIP and MEP over three trials. Mean MIP was 58 cm H20 (sd = 1.53) and mean MEP was 76 cm H20 (sd = 2.52), consistent with mild inspiratory and expiratory weakness, respectively. Lingual weakness was present and judged to be mild. This was similar to prior results obtained using the IOPI approximately six months prior in which the patient's mean lingual pressure was 38 kPa (sd = 2.65), consistent with mild lingual weakness. The Communicative Effectiveness Survey (CES) was administered at both visits and her score was 32/32 and 29/32, respectively, with a modal response of a 4 indicating the perception of effective communication.

VFSE showed mild oropharyngeal dysphagia with oral greater than pharyngeal dysphagia. Swallow signs on VFSE included slow oral transit, delayed tongue motion, and post-swallow pharyngeal residue. There was no penetration or aspiration. Lingual weakness was suspected as the underlying cause of many of her swallowing signs. A repeat evaluation in one year was recommended.

3. Discussion

Prior to the advent of ERT, oropharyngeal dysphagia did not receive substantial attention in patients with Pompe disease. The presence of feeding and swallowing difficulties in affected infants is well known [24–26], but the introduction of ERT and improved survival has made it a more critical issue. Dysphagia screening is now recommended as the standard of care for infantile-onset Pompe disease [1]. Additionally, motor speech deficits, which commonly co-occur with dysphagia, have been described [27]. There are no prior reports detailing oropharyngeal dysphagia in LOPD, although a single case report from 1993 describes bulbar weakness in LOPD [28].

Prior descriptions of LOPD have focused on proximal and respiratory muscle weakness, which are the most prominent features. More recent publications report other associated conditions that may negatively impact quality of life and mortality include ptosis [9–13], arteriopathy [29], and impaired gastrointestinal function [15]. Another review notes the occurrence of macroglossia, abnormal speech, cerebral aneurysms and one patient with feeding problems [30].

Dubrovsky et al. recently reported lingual weakness via manual muscle strength testing in 19 consecutive subjects with LOPD including two with asymptomatic disease and a positive family history [17], a novel observation. Our results are consistent with these prior findings. We encountered lingual weakness in all three patients. Patients with lingual weakness are at increased risk for dysarthria and dysphagia and evaluation for tongue weakness is now a standard part of our clinical evaluation and should be considered as part of the disease management guidelines [1].

In this retrospective review, 3 of 12 of LOPD patients reported bulbar symptoms at routine clinic visits. No other contributing illnesses causing dysphagia were identified. The severity varied in each of the 3 cases, but matched patients' overall status. Their symptoms are well aligned with the vacuolar myopathy described in bulbar musculature and the upper esophagus on prior pathologic reports [18,31,32]. The development of symptoms while receiving ERT may reflect a regional differential response in the bulbar musculature or unrecognized neurologic factors. It may seem surprising that dysphagia has not been reported more frequently, but mild difficulties with swallowing may not be reported by adult patients facing larger challenges with respiration and ambulation. Screening of all patients with LOPD for oropharyngeal dysphagia may reveal that the problem is more widespread than currently recognized.

As previously described, there was variance in the mechanism of dysphagia, correlating with the patients' overall clinical severity. Although histologic correlation is not available, these differences likely reflect the relative involvement of the respective muscle groups. It is reasonable to think that increasing clinical severity would correlate with increasing involvement of the bulbar musculature, however the extent and pattern of involvement in LOPD is variable for other muscle groups. Similarly affected patients in the cohort ($n = 12$) did not report symptoms. Aside from tissue biopsy, magnetic resonance imaging studies might be helpful in determining the extent of myopathic change in the genioglossus as demonstrated in an earlier publication [17,33].

The exact prevalence of dysphagia in LOPD is unknown and the cases here are of patients who self-reported their

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symptoms. This emphasizes that the LOPD phenotype is incompletely delineated. As a result of this experience, the clinical evaluation at our institution has recently been modified to actively screen for dysphagia and lingual weakness at each clinic visit. Although it is too early to know the impact of this screening, more patients with dysphagia will likely be identified. Future multicenter projects are needed to address the prevalence of dysphagia in LOPD, along with the effects of timely intervention.

Conflict of interest

Dr. Kishnani has received research/grant support and honoraria from Genzyme Corporation and Amicus Therapeutics. She is also a member of the Gaucher Disease Registry Board for Genzyme Corporation.

Dr. Hobson-Webb has received past salary support for performing neurologic examinations on patients participating in a clinical trial for Gaucher disease, sponsored by Genzyme Corporation. She has also received funding from the American Association of Neuromuscular and Electrodiagnostic Medicine Foundation for the study of peripheral nerve ultrasound.

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