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The emerging phenotype of late-onset Pompe disease: A systematic literature review

Justin Chan [a], Ankit K. Desai [a], Zoheb B. Kazi [a], Kaitlyn Corey [a], Stephanie Austin [a], Lisa D. Hobson-Webb [b], Laura E. Case [c], Harrison N. Jones [d], Priya S. Kishnani [a,*]

[a] Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center, Durham, NC, USA
[b] Department of Neurology, Division of Neuromuscular Medicine, Duke University Medical Center, Durham, NC, USA
[c] Doctor of Physical Therapy Division, Department of Orthopedics, Duke University School of Medicine, Duke University, Durham, NC, USA
[d] Department of Surgery, Division of Head and Neck Surgery & Communication Sciences, Duke University, Durham, NC, USA

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ABSTRACT

Background: Pompe disease is an autosomal recessive disorder caused by deficiency of the lysosomal glycogen-hydrolyzing enzyme acid α-glucosidase (GAA). The adult-onset form, late-onset Pompe disease (LOPD), has been characterized by glycogen accumulation primarily in skeletal, cardiac, and smooth muscles, causing weakness of the proximal limb girdle and respiratory muscles. However, increased scientific study of LOPD continues to enhance understanding of an evolving phenotype.
Purpose: To expand our understanding of the evolving phenotype of LOPD since the approval of enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme™/Lumizyme™) in 2006.
Methods: All articles were included in the review that provided data on the charactertistics of LOPD identified via the PubMed database published since the approval of ERT in 2006. All signs and symptoms of the disease that were reported in the literature were identified and included in the review.
Results: We provide a comprehensive review of the evolving phenotype of LOPD. Our findings support and extend the knowledge of the multisystemic nature of the disease.
Conclusions: With the advent of ERT and the concurrent increase in the scientific study of LOPD, the condition once primarily conceptualized as a limb-girdle muscle disease with prominent respiratory involvement is increasingly recognized to be a condition that results in signs and symptoms across body systems and structures.

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* Corresponding author at: Duke University Medical Center, 905 South LaSalle Street, GSRB1, Durham, NC 27710, USA.
E-mail address: jchan532@gmail.com (P.S. Kishnani).

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1. Introduction

Pompe disease (acid maltase deficiency, glycogen storage disease type II, OMIM ID: 232300) is an autosomal recessive disorder caused by deficiency of the lysosomal glycogen-hydrolyzing enzyme acid α-glucosidase (GAA OMIM ID: 606800), resulting in glycogen accumulation primarily in skeletal, cardiac, and smooth muscle [1–4]. The clinical spectrum of Pompe disease varies broadly, with significant differences existing in age of onset, rate of disease progression, and overall clinical phenotype. (See Tables 1 and 2.)

Pompe disease represents a continuum of disease spectrum, but in clinical practice two broad subtypes are recognized based on the presence or absence of cardiomyopathy and whether the onset of symptoms is prior to or after one year of age. In classic infantile-onset Pompe disease, GAA activity is absent (or nearly so) and the disease manifests shortly after birth, progressing rapidly to cardiorespiratory failure and death, usually within the first year of life. Due to higher residual GAA activity, late-onset Pompe disease (LOPD) typically presents in adulthood, although cases can present as early as the first year of life. Adults with LOPD typically present with difficulties in ambulation and respiratory involvement [5]. Historically, LOPD has been conceptualized as a proximal limb-girdle myopathy with greater than expected respiratory involvement. However, over the last decade, understanding of the spectrum of phenotypic manifestations of LOPD has broadened substantially. This spectrum includes bulbar muscle involvement manifesting as lingual weakness with dysarthria and dysphagia [6–8], osteoporosis [9,10], scoliosis [11,12], rigid spine syndrome (RSS) [13], sleep apnea and sleep disordered breathing (SDB) [14], small-fiber neuropathy (SFN) [15], sensorineural hearing loss [16], cerebral and intracranial aneurysms [17,18], cardiac hypertrophy, abnormal cardiac rhythm [19], impaired gastric function and GI motility [20,21], lower urinary tract (LUT) and anal sphincter involvement [20,22,23], pain [24], and fatigue [25].

Pompe disease severity varies by age of onset, extent of organ involvement, degree of myopathy, and rate of progression [6,25]. The progressive nature of the disease is reflected by the fact that the duration since symptom onset is typically a better predictor than age of disease. Severity and effects on quality of life, than age. Individuals with longer disease duration generally exhibit greater overall disease severity and diminished quality of life [2].

The variable clinical manifestations, broad phenotypic spectrum, rare nature of the condition, and the overlap of signs and symptoms with other neuromuscular diseases make the prompt diagnosis of LOPD challenging [26]. Conditions that are most frequently considered in the differential diagnosis include the limb-girdle muscular dystrophies; Becker muscular dystrophy; facioscapulohumeral muscular dystrophy; scapuloperoneal syndromes; rigid spine syndrome; myasthenia gravis; spinal muscular atrophy; polymyositis; fibromyalgia; chronic fatigue syndrome; glycogen storage diseases types IIIa, IV, V, and VII; Danon disease; rheumatoid arthritis; and mitochondrial myopathies [19,27].

Residual GAA enzyme activity detected in skin and muscle biopsy has traditionally been used to diagnose LOPD [26]. Measuring acid alpha-glucosidase activity in blood (leukocytes, lymphocytes, or dried-blood spot [DBS]) is now being increasingly utilized due to its reliability, cost-effectiveness, and its less invasive and time-consuming nature [26]. Selective screening for LOPD with the use of DBS assays, in individuals with asymptomatic elevated creatine kinase (CK) or hyperCKemia, has allowed the identification of affected individuals with LOPD [28–30]. For example, Musumeci and colleagues evaluated 1051 individuals in which 30 (2.9%) were diagnosed with an initial DBS screening. Similarly, 232 individuals (7.6%) of a sample of 3076 individuals with limb girdle muscle dystrophy and hyperCKemia were found to have low GAA activity with DBS [31,32].

There are several reports that characterize the clinical phenotype of infantile-onset Pompe disease [4,6,33–40]. The objective of this review is to provide a comprehensive review of the signs and symptoms of LOPD reported in the literature, awareness of which has expanded since the advent of ERT, in order to raise awareness of the multiple organ systems that may be involved in individuals with LOPD, as well as the variable presentation of individuals across the disease spectrum, in order to expedite diagnosis and treatment.

2. Methods

An electronic literature search of the PubMed database was performed for current and past findings of LOPD for the years 2006 through 2016 using the keywords “acid alpha-glucosidase deficiency”, “acid maltase deficiency”, “Pompe disease symptoms”, “adult-onset acid maltase deficiency”, along with the key clinical symptoms of LOPD, as described below. The publications selected were based on whether they reported new or relevant clinical manifestations since the approval of ERT in 2006. When there were overlaps between multiple studies, the more relevant articles were used. Some references prior to 2006 were included for informational and historical purposes. The study was organized based on the prevalence of each body system reported in the disease, such as muscular, respiratory, and musculoskeletal first, and less frequently reported systems such as neurological, vascular, and gastrointestinal in subsequent sections. Within each body system are subsections that describe the prevalence of reported symptoms and diagnoses based on the strength of evidence in the literature and personal experience. Lastly, individual case studies were also incorporated to include rare symptoms and manifestations reported in LOPD.

3. Results

A total of 213 articles on Pompe disease were found between 2006 and 2016 based on the search described in Methods. One article was discarded for being in another language, 52 animal studies were discarded, and 30 articles were discarded due to information overlap. Thus, including 38 informational and historical articles published prior to 2006, the total number of studies included in this review was 130. This article describes the various systems and manifestations involved in LOPD, including muscular, respiratory, musculoskeletal, neurological, vascular, cardiac, gastrointestinal, and psychiatric.

Table 1
Characterizations of body systems associated with reported LOPD symptoms and manifestations.

System	Symptoms and manifestations

Muscular	• Proximal muscles generally weaker than distal
	• Lower extremities generally weaker than upper
	• Weakness common in:
	  • Pelvic girdle / lower extremity musculature (psoas/hip flexors, hip extensors, hip abductors, hip adductors, with early involvement of adductor magnus and semimembranosus; later involvement of long head of the biceps femoris and semitendinosus; prominent involvement of vastus intermedius, vastus medialis, and vastus lateralis; and sparing of sartorius, rectus femoris, gracilis, and peripheral portions of vastus lateralis)
	  • Trunk muscles [paraspinal muscles, ventrolateral trunk muscles (abdominals), rectus abdominis]
	  • Shoulder girdle musculature and scapular stabilizers [deltoids, supraspinatus, trapezius inferior, rhomboids, subscapularis muscles. serratus anterior]
	  • Neck flexors typically weaker than neck extensors
	  • Respiratory muscles [diaphragm, upper respiratory muscles, inspiratory muscles of the chest, abdominals]
	  • Bulbar muscles [tongue (genioglossus), structures of oral cavity, velum (soft or muscular palate), pharynx, upper esophageal sphincter]. Dysarthria, oropharyngeal dysphagia [swallowing difficulties], hypernasal speech, or low volume speech may be present
	  • Facial muscles: [unilateral or bilateral ptosis (drooping eyelid(s), ophthalmoplegia (weakness/paralysis of extraocular muscles) with inability of eyes to fixate on one point)]
	• Exercise intolerance
	• Decreased endurance
	• Fatigue
	• Compensatory movements / deviations may include:
	  Beevor sign, positive Trendelenburg's sign, waddling gait, use of modified Gower's maneuver
	• Functional losses can include loss of ambulation, loss of independent transitions between positions, loss of independent breathing, difficulty with activities of elevation against gravity, difficulty with bed mobility, difficulty with lifting; and specific task specific individual functional losses

Respiratory	• Sleep apnea, sleep disordered breathing (SDB)[a] • Decreased vital capacity • REM sleep hypopneas with/without hypoventilation, sleep hypoventilation • Diaphragm weakness • Shortness of breath/decrease in FVC greater in supine vs upright • Impaired cough • Dyspnea
Musculoskeletal	• Osteoporosis, osteopenia, low bone mineral density (BMD) • Imbalance in bone remodeling • Compromised bone strength • Vertebral fractures • Scoliosis • Rigid spine syndrome (RSS) • Excessive kyphosis and/or lordosis and anterior or posterior pelvic tilt (details in text) • Limited flexion of neck and trunk, neck hyperextension, posterior (backward) or anterior (forward) trunk lean (posterior more common) • Chest wall abnormalities • Scapular winging
Neurological	• Small fiber neuropathy (SFN) • Sensorineural hearing loss (HL) (Impairment of stapedius muscle) • Orthostasis • Painful paresthesias in extremities • Muscle cramps • Dry eyes
Vascular	• Cerebral/intracranial aneurysms, aneurysmal thrombosis • Lacunar encephalopathy • Dolichoectasia of basilar artery • Microhemorrhages/intraparenchymal hemorrhage • Aortic abnormalities (dilated arteriopathy, thoracic and basilar aortic aneurysms, aortic stiffness, dilation of thoracic aorta)
Cardiac	• Cardiac hypertrophy (rare cardiomyopathy) • Abnormal heart rhythm (supraventricular tachycardia [SVT], Wolff-Parkinson-White [WPW] syndrome)
Gastrointestinal + genitourinary	• Hepatomegaly • Abdominal discomfort • Cramps • Constipation • Chronic diarrhea • Postprandial bloating • Early satiety • Poor weight gain/overweight • Decreased gag reflex • Urinary and bowel incontinence due to weakness of anal sphincter (stool urgency)
Pain and fatigue	• Muscle pain, cramps o Lower back o Shoulders o Upper legs/thighs • Mental/physical tiredness from muscle weakness • Exhaustion (fragmented sleep, daytime sleepiness)

[a] Note: information was adapted from all articles referenced in this review.

Table 2
Common missed or misdiagnosis in LOPD.

Study[a]	Misdiagnosis
How common is misdiagnosis in late-onset Pompe disease? [123]	• 11/23 LOPD individuals misdiagnosed with common symptoms: • Limb or leg weakness/myalgias: deconditioning, lumbar radiculopathy, lupus, muscle strain, musculoskeletal disease, polymyalgia rheumatica, polymyositis, polymyositis + fibromyalgia, postpolio syndrome, and psychogenic weakness. • Low back pain: deconditioning, muscle strain, postpolio syndrome • Exercise intolerance, headaches: obstructive sleep apnea • Mean diagnostic delay: 10 years.
Adult-onset acid maltase deficiency presenting as diaphragmatic paralysis [124]	• 51-year-old male initially diagnosed with diaphragmatic paralysis. Diagnostic delay: 6 years.
A 60-year-old woman with weakness, fatigue, and acute respiratory failure: case report and discussion of the differential diagnosis [125]	• Woman was initially diagnosed with hypoventilation secondary to neuromuscular dysfunction
Late onset glycogen storage disease type II: pitfalls in the diagnosis [126]	• 41-year-old female misdiagnosed with hypothyroid myopathy. Diagnostic delay: 20 years. • 45-year-old female misdiagnosed with connective tissue disorder. Diagnostic delay: 20 years. • 32-year-old male misdiagnosed with liver disease and possible hepatopathy. Diagnostic delay: 10 years. • 31-year-old male initially diagnosed with muscular dystrophy. Diagnostic delay: 20 years.
Pompe disease, the must-not-miss diagnosis: a report of 3 patients [127]	• 45-year-old male initially diagnosed with unspecified limb girdle muscle dystrophy. Diagnostic delay: 13 years. • 40-year-old male misdiagnosed with unspecified limb girdle muscle dystrophy with respiratory involvement. Diagnostic delay: 10 years. • 78-year-old female initially diagnosed with possible mitochondrial myopathy due to eyelid ptosis and muscle weakness. Diagnostic delay: 30 years.
The spectrum and diagnosis of acid maltase deficiency [128]	• Two adults were initially diagnosed with polymyositis. Five adults were diagnosed with muscular dystrophy. Mean diagnostic delay: 10 years.
Polymyositis: a common misdiagnosis for late onset Pompe disease (Kasturi, Jain et al. 2013) [abstract]	• 44-year-old male initially diagnosed with polymyositis. Diagnostic delay: 16 years.
Delayed diagnosis of late-onset Pompe disease in patients with myopathies of unknown origin and/or hyperCKemia [129]	• 63-year-old female initially diagnosed with limb girdle muscle dystrophy at 37 years/old due to proximal muscle weakness, myopathic gait, dysphagia, and DOE. • 61-year-old female initially presented proximal muscle weakness in arms and lower limbs. Diagnostic delay was 9 years.
LOPED study: looking for an early diagnosis in a late-onset Pompe disease high-risk population [28]	• Total screened individuals: 1051 • Among 17 misdiagnosed individuals, the mean age of symptom onset was 40 ± 14.3 years. • 65% (11 individuals) were initially diagnosed with hyperCKaemia and limb girdle muscle weakness • 29% (5 individuals) were initially diagnosed with isolated hyperCKaemia. • 6% (1 individual) were initially diagnosed with limb girdle muscle weakness. • Mean diagnostic delay was 7 years.

[a] Note: previous studies describing initial misdiagnoses, total screened individuals (if relevant), method used to achieve Pompe diagnosis, and total diagnostic delay.

3.1. Muscular manifestations

In LOPD, the most common signs and symptoms include proximal limb-girdle weakness, trunk weakness, impaired mobility, exercise intolerance, fatigue, and difficulty performing activities of elevation against gravity [13,18]. On physical examination, individuals may demonstrate reduced proximal limb strength, a positive Trendelenburg's sign (pelvis drops on the side opposite to the stance leg due to weakness in hip abductors on the stance side when standing on one leg), postural alterations during gait, and use of a modified Gower's maneuver (hands and arms used to "walk" up their own body from a squatting position due to lack of hip and thigh muscle strength) and difficulty climbing stairs [19,41,42]. The initial clinical presentation of individuals with LOPD is often impaired motor function and is difficult to diagnose due to it resembling a myriad of other neuromuscular disorders. The specific patterns of muscle involvement were described historically by observation and have been clarified further by whole body magnetic resonance imaging (WBMRI), which has highlighted involvement of spinal extensors, subscapularis, and thigh musculature [43]. Primary muscular manifestations include involvement of the hip girdle/proximal lower extremity musculature, respiratory muscles, and trunk musculature including paraspinal muscles and abdominals. This triad is seen in approximately 80% of individuals diagnosed with LOPD [13,44]. In relation to abdominal muscle involvement, individuals with LOPD may occasionally show a Beevor sign, which is an abnormal upward movement of the umbilicus when attempting to raise the head from a supine position due to paralysis of the inferior portion of the rectus abdominal muscle [45].

3.1.1. Lower extremity manifestations

Muscle involvement in LOPD is dominated by progressive proximal > distal muscle weakness in the lower extremities more than the upper extremities [35]. Depending on the pattern and severity of muscle involvement, individuals may present with difficulty climbing stairs, playing sports, and running [19,46]. As the disease progresses, individuals exhibit difficulty raising their arms overhead, performing activities of elevation against gravity including getting upright after bending over, achieving standing from sitting, rising from a supine position, jumping, rising from a squatting position, lifting objects from the floor, and turning in bed.

Among pelvic muscles, weakness predominates in the hip extensors, adductors, and abductors, followed by psoas (hip flexors). Among femoral muscles, the weakness of the thigh adductors is greater than that of the thigh abductors, and the posterior thigh muscles are selectively affected. In the later stages of the disease, this selective pattern of involvement is less apparent among pelvic girdle and thigh muscles, with weakness more profound in most pelvic girdle musculature, while leg and foot muscles are spared or minimally involved [47,48]. This pattern is helpful in establishing a diagnosis of LOPD. Muscle MRI reveals that the most pronounced lower extremity abnormalities

(e.g., fatty infiltration, atrophy) are found in the posterior thighs, with early involvement of the adductor magnus and semimembranosus and later involvement of the long head of the biceps femoris and semitendinosus posteriorly [47]. Furthermore, there is prominent involvement of the vastus intermedius, vastus medialis, and vastus lateralis anteriorly, with sparing of the sartorius, rectus femoris, gracilis, and peripheral portions of the vastus lateralis [47,48].

Muscle MRI can provide useful diagnostic guidance for accurate assessment of muscular involvement, and show that fatty muscle degeneration may occur before muscle weakness manifestations. Therefore, a full body MRI may act as an initial diagnostic tool, as well as a biomarker to monitor disease progression [8,47,49]. Full body MRI could serve as an especially useful tool to distinguish LOPD from other muscle diseases, specifically limb girdle muscle dystrophies [43].

3.1.2. Respiratory muscle manifestations

Progressive respiratory muscle involvement in LOPD leads to increasingly severe pulmonary signs and symptoms, with respiratory failure the most common cause of death. Symptoms of respiratory involvement include fatigue, daytime sleepiness, headaches, and decreased sleep quality, which are signs of potential chronic respiratory insufficiency, decreased vital capacity and diaphragm strength, and acute respiratory failure [14,48,50–52]. Respiratory muscle weakness also contributes to cough inadequacy, threatening airway protection/secretion management and leading to recurrent respiratory infections and hospitalization.

Respiratory muscle weakness is very common in LOPD, affecting up to 80% of individuals with LOPD [41], and is typically present in both the inspiratory and expiratory musculature [50,53]. Assessments of upright and supine pulmonary function tests (PFTs) are necessary to determine the risk for respiratory compromise, and in many instances to identify early pulmonary involvement. PFT's have shown that diaphragmatic weakness in neuromuscular disorders is characterized by a postural drop in forced vital capacity (FVC) > 25% from the upright to supine position [51].

Due to its central role in ventilation, diaphragmatic weakness is considered to be the principal cause of respiratory dysfunction in LOPD [50]. As the disease progresses, hypoventilation develops during waking hours, and hypoxemia and cor pulmonale result in the end stages increasing the likelihood of death. Diaphragmatic weakness can be initially detected by symptoms of unrestful sleep, nocturnal awakening with dyspnea, and morning headaches due to nocturnal hypoventilation during REM-sleep, leading to sleep-disordered breathing (SDB) [5,6,54,55].

Recent imaging data provide further support for the pervasive involvement of the respiratory muscles in individuals with LOPD. Gaeta and colleagues in 2013 examined the correlations between results from MRI and CT imaging examinations and pulmonary function tests in 10 individuals with LOPD. Statistically significant correlations were present for grading of diaphragmatic atrophy on imaging and supine FVC, postural drop in FVC, peak cough flow (PCF), and maximum inspiratory pressure (MIP). Additionally, in 8 of the 10 participants, respiratory muscle involvement extended to include the musculature comprising the abdominal wall. Similarly, Wens and colleagues in 2015 obtained static spirometer-controlled MRI scans of the lungs during maximal inspiration and expiration in LOPD subjects and controls [56]. In comparison to controls, LOPD subjects demonstrated significantly smaller cranial-caudal length ratios highly correlated with supine FVC and FVC postural drop, indicating diaphragm weakness.

Respiratory muscle weakness contributes to SDB manifesting in the majority of individuals with concomitant diaphragmatic weakness [14,55]. SDB is reported to progress to nocturnal hypoventilation, manifesting as hypercapnia during sleep, and eventually diurnal respiratory failure. Symptoms of SDB include reduced sleep quality, excessive daytime sleepiness, dizziness, shortness of breath, and fatigue. Diagnoses include obstructive sleep apnea, REM sleep hypopneas with or without hypoventilation, and continuous sleep hypoventilation [14]. The degree of SDB and respiratory impairment correlate with diaphragm dysfunction, degree of ventilatory restriction, and daytime lung function, specifically exertional dyspnoea and dyspnoea at rest [14]. Adequate and timely use of non-invasive ventilator support (e.g. BiPAP), and pulmonary management, including airway clearance and use of cough assist devices, may be needed to optimize health.

Although individuals with LOPD utilize mechanical ventilatory support, respiratory failure remains a major cause of death [19,46]. For example, two individuals with compromised respiratory function based on PFTs both experienced a fall with inability to move once supine due to profound weakness, leading to presumed asphyxia and death from poor supine respiratory function [57]. Since motor function does not correlate well with respiratory function, individuals with LOPD may be in vulnerable positions of having the ability to ambulate, but unable to compensate from a respiratory standpoint if they suffer from a fall or attempt to become supine.

Due to the high prevalence of diaphragmatic weakness in LOPD, respiratory insufficiency is a serious threat and can be a primary presenting feature of Pompe disease [2,55]. In contrast to most other neuromuscular disorders, severe respiratory problems may precede limb muscle weakness in Pompe disease [14,48]. It is important to note that respiratory function does not consistently correlate with either skeletal muscle strength or gross motor function, but its involvement can be greater than the musculoskeletal system or be the primary manifestation [58].

3.1.3. Paraspinal muscles and scapuloperoneal manifestations

The most severely affected muscles in the trunk are the paraspinals, ventrolateral trunk muscles (abdominal obliques, intercostals, and transversus abdominis), and rectus abdominis, which often undergo atrophy and fatty degeneration [47]. Scapular winging and paraspinal muscle atrophy have also been observed [48,59]. Clinical myotonia is absent, but myotonic discharges on needle electromyography (EMG) testing may be evident, especially in the paraspinal muscles [60]. Myotonic discharges are an important feature of Pompe disease and may help in making the diagnosis [61]. Weakness has also been noted in the scapular girdle muscles, as well as the scapular fixators, specifically the trapezius inferior, rhomboid, and subscapularis muscles. Moderate involvement can be present in serratus anterior, deltoid, and supraspinatus muscles. Trunk extensors and abdominal muscles are frequently and markedly affected, neck flexor muscles and neck extensors are variably affected [62]. All distal upper limb muscles are minimally and infrequently involved, except in severe, advanced disease.

LOPD is characterized by a "waddling" gait with lumbar hyperlordosis [48]. Most recent data from gait analysis, report spatiotemporal gait deviations compared to typical gait secondary to weakness in the lower extremities and trunk muscles. Abnormalities in spatiotemporal gait parameters include decreased velocity and cadence, wider base of support, shorter step and stride length, and prolonged stance phase and time in double limb support. These signs are associated with instability in single limb support, difficulty during the swing phase of gait, increased risk of falls, and lack of energy efficiency associated with fatigue [63].

3.1.4. Facial and bulbar muscle weakness

In LOPD, accumulating data suggest that lingual weakness occurs relatively early and frequently in individuals with LOPD, and the bulbar musculature, particularly the tongue (genioglossus), is affected [7]. Lingual weakness can be a very early feature of Pompe disease, increasing risks for aspiration. A prior study on whole-body muscle MRI revealed marked involvement of the lingual musculature in 20 individuals with LOPD [43], which may lead to swallowing difficulties, dysphagia, and speech dysarthria.

Due to facial and lingual weakness, individuals with LOPD are at an increased risk for dysarthria and dysphagia [7,64]. Case studies provide the earliest suggestion of lingual weakness and dysarthria in individuals with LOPD [65–67]. In one study, an inverse correlation between facial

and lingual strength and dysarthria was reported; as dysarthria severity increased, facial and lingual strength decreased [7].

Oropharyngeal dysphagia, which is a specific type of dysphagia that involves abnormalities in muscles, nerves, or structures of the oral cavity, pharynx, and upper esophageal sphincter, has been reported in a few LOPD individuals [68]. Variance of dysphagia correlated with one's unique clinical severity, and also reflected involvement or weakness of each specific muscle group. Although the pattern of involvement in LOPD is variable for each muscle group, increasing clinical severity is hypothesized to correlate with increasing involvement of the bulbar musculature [61,68]. Currently, the low reported rates of oropharyngeal dysphagia may be due to individuals with LOPD experiencing larger challenges inhibiting quality of life, such as respiration and ambulation issues, preventing dysphagia from being prioritized [68].

The mounting evidence of bulbar muscle involvement in LOPD underscores the need for more research to determine functional effects, temporal progression, and effects of treatment [21,68]. Due to consistent findings of dysphagia, and dysarthria in LOPD, examination of tongue strength and lingual are necessary for all individuals with Pompe disease due to the numerous potential functional consequences [27].

3.1.5. Ptosis and other eye findings

Individuals with LOPD often have ptosis as the presenting feature [69,70]. For example, a 45-year-old woman presented two main clinical features: bulbar paresis and ptosis, and had a delayed diagnosis of 10 years [70]. Another study reported one individual out of a cohort of 28 patients with LOPD who had severe bilateral ptosis [71]. Ophthalmoplegia, the paralysis of the muscles within or surrounding the eye, can present in other neuromuscular disorders, including myasthenia gravis and mitochondrial myopathies, has rarely been observed in LOPD [17,72]. Although glycogen is ubiquitous throughout the body, its accumulation in the lens and retina could potentially lead to cataract formation and aberrant retinal function, respectively. Ptosis and ophthalmoplegia should be recognized as potential features of the disease; therefore all individuals with Pompe disease should undergo ophthalmologic examination [70,73].

3.2. Musculoskeletal manifestations

Individuals with LOPD exhibit a variety of musculoskeletal manifestations, primarily osteoporosis and increased incidence of fractures, scoliosis, rigid spine syndrome (RSS), other spine abnormalities including kyphosis and lumbar lordosis due to underlying muscle weakness, and decreased muscle flexibility and extensibility [11–13,62,74–77].

3.2.1. Osteoporosis and increased incidence of fractures

Osteoporosis is a common feature in Pompe disease often exhibited as an imbalance in bone remodeling, compromised bone strength, higher risk of fractures, especially in individuals who are wheelchair-bound and ventilator dependent [9,10]. Furthermore, low bone mineral density (BMD), osteopenia, and osteoporosis have been observed in ambulant individuals with LOPD, indicating that factors other than immobilization and inactivity, such as decreased muscle strength, contribute to the development of osteoporosis. Normal muscle function and normal weight bearing are required to maintain a healthy skeleton [4,35], therefore decreases in BMD may be due to a lower mechanical load applied on bones by weakened muscles, and decreased weight bearing [9,78]. Although osteopenia does not directly result in fractures, it increases the risk of traumatic fractures when combined with physical impairment and falls, both of which are features of individuals with Pompe disease. Conversely, Bertoldo and colleagues reported that fracture risk is likely to be independent from muscular and respiratory phenotype in LOPD, and the high risk for vertebral facture seems to be independent of the clinical phenotype and genotype.

3.2.2. Scoliosis

Scoliosis is identified as an abnormal lateral curve of the spine (>10° deviation with a rotational deformity) and chest wall abnormalities [11], and is found in individuals with Pompe disease of varying ages. It is more frequently observed in early onset and wheelchair-dependent individuals with Pompe disease [12]. From an analysis of the Pompe Registry, scoliosis was present in 33% of all individuals with LOPD, more frequently in children (57%) and juveniles (52.9%) than adults (24.8%) [11]. Scoliosis in individuals with Pompe disease is detrimental as it contributes to reduced pulmonary function, increases the need for respiratory support, and can contribute to pain and risk of compromised skin integrity, especially in non-ambulatory individuals as in other neuromuscular disorders. Excessive kyphosis and lordosis are both reported in LOPD, and may differ when standing versus sitting, similar to many neuromuscular disorders. Excessive kyphosis, which is an exaggerated rounding of the back, may occur in the thoracic region, or the lumbar region in which it would be accompanied by a posterior pelvic tilt, or present throughout. Kyphosis is common in many neuromuscular disorders, associated with trunk and proximal muscle weakness and vertebral fractures [79–81]. Excessive lordosis, or excessive spinal extension, may occur most frequently in the lumbar region in which it is accompanied by an anterior pelvic tilt, and is due to abdominal and hip extensor weakness. Excessive kyphosis at one level may be combined with excessive lordosis at other levels. Roberts, Kishnani et al. in 2011 reported that individuals from the Pompe Registry, which was composed of a majority of individuals with LOPD, when diagnosed with scoliosis, typically have abnormal kyphosis and lordosis [11]. Clinical assessment for scoliosis should be regularly performed for all individuals with Pompe disease.

3.2.3. Rigid spine syndrome (RSS)

Rigid spine syndrome (RSS) is a progressive limitation of flexion of the neck and trunk leading to non-painful postural anomalies [74]. Individuals with RSS typically present with neck hyperextension and forward trunk tilt, with flexion possible only at the hips. It is suggested that RSS is under-recognized in LOPD due to the frequent involvement of truncal muscles in LOPD, especially in relation to scoliosis [13]. In some instances, RSS has been reported as the primary presenting feature in individuals with Pompe disease; therefore Pompe disease should be considered in the differential diagnosis of RSS [19,62,75,76].

Due to the high prevalence of asymptomatic vertebral fractures in individuals with LOPD, spinal X-rays should be routinely performed regardless of disease severity [77].

3.3. Nervous system involvement

Prior literature has reported accumulations of lysosomal glycogen in the central and peripheral nervous system. Autopsy studies have demonstrated glycogen accumulation in the brain, brainstem nuclei, and anterior horn cells [4]. Evidence of specific neurological involvement includes small-fiber neuropathy, and sensorineural hearing loss in LOPD [82].

3.3.1. Small-fiber neuropathy

Small-fiber neuropathy (SFN), which affects myelinated and unmyelinated nerves responsible for pain and temperature sensation, cause afflicted individuals to experience painful paresthesias in the extremities, muscle cramps, orthostasis, gastrointestinal dysfunction, dry eyes, and sexual dysfunction [83,84]. Pompe disease is reported to be a cause for SFN due to glycogen deposition in the Schwann cells of peripheral nerves. There have been anecdotal reports of limb pain and alterations in heart rate [15]. Previously, Origuchi and colleagues had described glycogen storage in fibers of peripheral nerves, as well as in Schwann cells in the material of sural nerve biopsy. Fidzianska and colleagues have demonstrated the appearance of intralysosomal glycogen in some muscle fibers and in the axons of intramuscular nerves from

an individual with LOPD [85,86]. Furthermore, SFN was confirmed via skin biopsies in two individuals [82]. The first individual exhibited frequent swellings of the epidermal nerve fibers, consistent with axonal degeneration, and had a score of 29 on the Small-Fiber Neuropathy Screening List (SFNSL), which is a 21-item list where a score of ≥11 is considered to be a positive screen. The second individual exhibited loss of epidermal nerve fiber density and an absence of intraepidermal nerve fibers at the distal calf site. In a subsequent screening, 22 (50%) of 44 total individuals with LOPD scored ≥11 on the SFNSL, supporting the clinical evidence suggesting neuropathic involvement in LOPD [82]. Identification of small-fiber neuropathy (SFN) would be important in the care and treatment of LOPD not only due to the morbidity associated with neuropathic pain but also its presence alerting the physicians of the potential autonomic dysfunction [82].

3.3.2. Hearing loss

Sensorineural hearing loss (HL) has been reported in individuals with LOPD [87]. The prevalence of sensorineural HL in LOPD is comparable to its prevalence in the general population, but slightly exceeds the normative data of the general population when adjusted for age and gender [16]. Other mechanisms that may contribute to HL in LOPD is the impairment of the stapedius muscle, which is a skeletal muscle in the tympanic cavity of the middle ear and is likely to be affected by glycogen accumulation.

3.4. Vascular manifestations

Cerebral and intracranial aneurysms are recognized as emerging features of LOPD. Vacuolar degeneration and glycogen deposits in vessel walls of cerebral arteries diminish smooth muscle integrity, possibly leading to the occurrence of dilatative arteriopathies or aneurysms in LOPD [18,88,89].

Although cerebral vasculopathies may be primary presenting features in LOPD, manifesting as aneurysms, microhemorrhages, and dolichoectasia of the basilar artery, the reported prevalence of cerebral vasculopathies still may be underreported [90–92]. Zhang, Zhao et al. in 2016 reported cerebral aneurysms among eight individuals with LOPD but in a more recent report, with the use of cerebral CT angiography (CTA), intracranial arterial abnormalities were reported in 13 of 21 individuals with LOPD, including unruptured intracranial aneurysms (2/21), vertebrobasilar dolichoectasia (10/21), and basilar artery fenestration (1/21) [89,93]. These 13 individuals exhibited signs of lacunar encephalopathy, such as insular, capsular, and frontal subcortical lesions, which correlated with respiratory impairment and may represent hypoxic-ischemic origins.

Dolichoectasia of the basilar artery and internal carotid dilatative arteriopathy are present in 0.06% to 5.8% of the general population [90,94], but have been reported in four of six individuals with LOPD screened with magnetic resonance angiography (MRA) [91]. In the same study, dolichoectasia of the basilar artery has been associated with left cranial nerve or oculomotor nerve dysfunction, and transient ischemic attacks [91]. Lastly, dolichoectasia may occur in individuals afflicted with other hereditary disorders, such as AIDS, sickle cell disease, Marfan syndrome, Ehlers-Danlos syndrome, and Fabry disease, causing potential misdiagnoses [90].

The cerebral vascular abnormalities may be predominantly due to posterior vascular circulation involvement, such as a weak intracranial arterial elastic layer that is more vulnerable to the formation of aneurysm expansion and vascular disease [89,95]. Young and middle-aged individuals with aneurysms, headaches, dizziness, cerebral vascular morphology changes, and unexplained dilative arteriopathy of intracranial, vertebral and basilar arteries, should be tested for Pompe disease even if there has been no loss of ambulation. Similarly, as part of the history gathering in patients with LOPD these questions should be asked.

Lastly, aortic abnormalities have been found in individuals with LOPD. Evidence of dilated arteriopathy involving primarily the ascending thoracic aorta was reported in five females with LOPD. One individual had a bicuspid aortic valve and developed dissection. Another individual with juvenile onset disease had both thoracic and basilar aortic aneurysms [96]. Increased aortic stiffness and smooth muscle involvement in some individuals with LOPD has been reported. The cardio cerebrovascular pattern is caused by changes in the smooth muscle cells by the accumulation of glycogen, which results in aortic stiffness, dilation of thoracic aorta, and dolichoectasias in cerebral arteries [13].

3.5. Cardiac manifestations

Cardiac involvement in Pompe disease was previously recognized only in infantile cases, but cardiac hypertrophy, heart rhythm disturbances, and aortic abnormalities are now also recognized in LOPD [90–96]. The differences in prevalence and severity of cardiac involvement in individuals with IPD versus LOPD is due to the higher amount of residual acid alpha-glucosidase activity in adults, and the differences in storage capacity and metabolism of heart and skeletal muscle [97,98].

3.5.1. Cardiac hypertrophy

Although Soliman and colleagues observed left ventricle dysfunction and hypertrophy in 46 individuals with LOPD, there were no major cardiac abnormalities. These cardiac abnormalities, which included isolated low systolic mitral annular velocities and mild left ventricular diastolic dysfunction, could be explained by a history of hypertension and/or advanced age [99] and were not clearly the result of LOPD. Forsha and colleagues also reported limited cardiac involvement in 87 individuals with LOPD, such as left ventricular hypertrophy, short PR interval on ECG, and decreased ejection fraction on echocardiogram [100]. Additionally, Morris and colleagues demonstrated that individuals with LOPD had similar structural and functional myocardial features in comparison to healthy subjects. There was also a lack of evidence showing LOPD populations developing valvular cardiac alterations, ECG abnormalities, or myocardial fibrosis [52].

Although the current evidence suggests that there is minimal cardiac involvement in LOPD, there are cases of individuals with LOPD with cardiomyopathy [101–103]. Therefore, cardiomyopathy and cardiac hypertrophy still needs to be recognized as a possible LOPD clinical feature although it is not as common as in IPD.

3.5.2. Abnormal heart rhythm

Different types of cardiac arrhythmias have been observed, some with more common and unspecific sinus arrhythmias, while others with more specific arrhythmias, including supraventricular tachycardia (SVT), sick sinus syndrome, Lown IVb ventricular arrhythmia, and especially WPW syndrome [13,19,50,99,100,104,105]. WPW syndrome is reported in both IPD and LOPD, possibly due to the disruption of the annulus fibrosis by glycogen-filled myocytes allowing ventricular preexcitation [106–108]. Furthermore, WPW is also associated with SVT; one study reported that several individuals with histories of WPW syndrome experienced recurrent SVT episodes, requiring hospital admission [100]. Individuals with LOPD may present with cardiomyopathies even in the absence of skeletal muscle involvement; therefore, screening for patients with LOPD with ECGs and echocardiograms is highly recommended.

3.6. Gastrointestinal and genitourinary manifestations

Gastrointestinal (GI) symptoms may be the presenting symptoms of LOPD, and include abdominal discomfort, chronic diarrhea, cramps, constipation, postprandial bloating, early satiety, feeding and swallowing difficulties, poor weight gain, and decreased gag reflex [4,20,22]. For example, two sisters had fibromyalgia-like pain associated with irritable bowel syndrome. Their diagnosis of LOPD was confirmed genetically,

and although their GI symptoms improved with ERT, pain persisted [109].

There are also issues with the genitourinary (GU) system, which may be due to glycogen accumulation in smooth muscle tissues. Primary symptoms, including bowel and urinary incontinence, such as stool urgency and diarrhea, are found in individuals with weaker limb strength and lower vital capacity, and has been reported during all stages of LOPD, significantly interfering with their quality of life [22,110]. For example, stool urgency, diarrhea, and urinary urge incontinence were reported significantly more frequently in individual with LOPD (55%, 56%, 33%) compared to general population age and gender-matched controls (20%, 18%, 7%) [110,111]. In conclusion, individuals with LOPD often experience issues with the GI and GU systems, which are often overlooked although they have major impacts on quality of life.

Future investigations are needed to determine underlying mechanisms, frequency, and severity of the gastrointestinal symptoms in LOPD, as well as their response to ERT. Such studies include histologic analyses in order to explore the role of smooth muscle glycogen accumulation [20,112].

3.7. Pain and fatigue

Although symptoms related to limb-girdle weakness are the most common presenting features, individuals with LOPD may experience muscle pain, muscle cramps, or low back pain [19,46]. Pain and fatigue are not related to disease duration, but could be initial manifestations of the disease, and are difficult indications to define and measure due to their non-specific, subjective, and complex nature [46].

Pain in individuals with LOPD has been found to be related to reduced quality of life, less participation in daily life, and greater depression and anxiety [24]. Questionnaires such as the Brief Pain Inventory [113] and the Pain Severity Score [114] are commonly utilized to assess the presence and severity of pain. Pain is primarily found in the back, shoulders, and the upper legs and thighs, and has been found to be twice as prevalent in individuals with LOPD in contrast to individuals without LOPD [24]. Causes of pain include postural problems from mechanical stress, muscle pain, and pain from fatigue, which may all require individual assessment to identify potential causes and interacting factors and to identify appropriate and successful individualized therapeutic approaches which may differ depending on contributing factors.

Fatigue can have a profound and disabling impact on the lives of individuals with LOPD. Two possible definitions of fatigue are extreme and persistent mental and/or physical tiredness, weakness or exhaustion [115], and difficulty in initiating or sustaining voluntary activities [116]. The self-report questionnaire, Fatigue Severity Scale (FSS), is utilized to measure fatigue as it focuses on the physical symptoms, as well as the severity. Fatigue most likely results from muscle weakness, especially in respiratory muscles, leading to fragmented sleep, which may result in daytime sleepiness [54]. Optimizing function and use of assistive technology, adapted function, and energy conservation may be important [35].

3.8. Psychiatric challenges

Individuals with LOPD may also experience mental health difficulties due to a variety of factors, including coping with this chronic illness, reduced family roles, financial issues, and fatigue inhibiting them from performing daily physical activities, such as walking, running, and walking up stairs [24]. Several studies have characterized a relationship between fatigue and depression in neurological disorders [116–120]. Symptoms of depression have been assessed using the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) (range from 0 to 21) [24,121,122]. HADS is widely used in different disorders and demonstrates reliability and validity [122].

Further research is needed to clarify the underlying mechanisms behind the direct or indirect effects ERT has on mental health. Decreased depression has been found to inversely correlate with improvements in fatigue due to ERT, but not significantly with changes in muscle strength or pulmonary function [121].

4. Conclusion

As described, there is a wide phenotypic spectrum for LOPD. In an effort to clarify the emerging phenotype of LOPD, this comprehensive review describes the expanded features of LOPD identified in the literature since the approval of ERT with alglucosidase afla in 2006, allowing better disease recognition from improvements in survival rates and clinical outcomes. This article details the symptoms and indicators of the disease. As more individuals with Pompe are diagnosed and monitored in clinics, it is clear that LOPD causes more than proximal myopathy and respiratory failure; it is a multisystemic disease involving muscular, respiratory, musculoskeletal, peripheral nervous, vascular, cardiac, and gastrointestinal systems. The most common symptoms reported in LOPD include proximal muscle weakness, trunk muscle weakness, exercise intolerance, shortness of breath, impaired cough, and gait difficulties. Due to the fact that LOPD is a multisystemic disease, clinicians should be aware of all known symptoms and indicators in order to prevent delayed diagnoses and misdiagnoses. The natural history and understanding of LOPD is evolving with the use of ERT, and the natural history of LOPD is now developing as a treated disease, as we have seen with IPD, due to increased survival rates and prolonged life expectancies [33].

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