



Multisystem presentation of Late Onset Pompe Disease: what every consulting neurologist should know

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ABSTRACT

Introduction. Pompe Disease is a rare, autosomal recessive, lysosomal disorder caused by deficiency of alpha glucosidase (GAA). It leads to the accumulation of glycogen in body tissues, with severe myopathy and cardiomegaly as a hallmark of the classic infantile form. Non-classical, or Late Onset Pompe Disease (LOPD) manifests after 12 months of age or in adulthood.

Material and methods. The clinical heterogeneity of LOPD causes delay in diagnosis and pharmacological treatment. In the Polish population, it is still underdiagnosed, and the time from onset to diagnosis remains a cause for concern.

Clinical implications. Although typically patients present with proximal muscle weakness, high CK or early respiratory insufficiency, they can also suffer from multiple symptoms from other organs. Patients may present with arrhythmias, vascular abnormalities including aneurysms or dilative arteriopathy, gastric or urinary symptoms, or musculoskeletal pathologies.

Results. A high index of suspicion among neurologists consulting internal medicine wards would aid early diagnosis of LOPD, while a multidisciplinary approach with the involvement of other specialists can reduce the risk of complications and improve the prognosis for LOPD patients. Patients who manifest with musculoskeletal and respiratory symptoms are prone to be diagnosed sooner than individuals with non-muscular symptoms, and therefore it is important to raise awareness of other manifestations of this disease.

Key words: LOPD, Late Onset Pompe Disease, GAA, multidisciplinary approach

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Introduction

Pompe Disease (PD, glycogen storage disease type II; OMIM # 232300) is a rare neuromuscular disease caused by mutations of the acid α -glucosidase (GAA) gene encoding acid maltase, transmitted as an autosomal recessive disorder. GAA deficiency leads to the accumulation of glycogen in body tissues, with a predilection for the skeletal muscles [1, 2].

The classic infantile form (Infantile Onset Pompe Disease, IOPD) presents within the first year of life, while the non-classical form, or Late Onset Pompe Disease (LOPD), becomes symptomatic between 12 months of age and late adulthood [1, 3]. IOPD has a rapidly progressive course with severe cardiomegaly, hepatomegaly and myopathy. Without pharmacotherapy, it leads to death before the second birthday [4].

LOPD is heterogeneous clinically and poses a significant diagnostic challenge, especially when pulmonary or cardiac symptoms are present before significant skeletal muscle weakness. The most common symptoms of LOPD are listed in Table 1.

The incidence of Pompe Disease is estimated at approximately 1:40,000 — 1: 60,000 [5–9]. With its unspecific phenotype, LOPD is still underdiagnosed in many populations [1, 10].

Enzyme replacement therapy (ERT) for Pompe Disease with alpha glucosidase was approved in 2006. Early treatment improves the patients' prognosis, allowing them to improve or maintain their respiratory functions and ambulation, and lowering their mortality rate [11–14].

Pompe Disease is a multisystem condition. Due to its heterogeneous disease presentation, in this article we seek

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Table 1. Most common symptoms in LOPD patients

Affected system	Most common symptoms
Laboratory findings	CK, LDH, AST, ALT elevation
Neuromuscular symptoms	Limb girdle muscle weakness Axial muscle weakness Frequent falls Difficulties in climbing stairs Myalgia Fatigue
Musculoskeletal and bones symptoms	Spine abnormalities: scoliosis, kyphosis and lumbar lordosis Rigid spine syndrome Osteoporosis and bone fractures Asymptomatic vertebral fractures
Respiratory symptoms	Sleep disruption Fatigue, excessive daytime sleepiness, nocturnal hypoventilation, orthopnoea Wheezing Morning headache Impaired coughing Frequent airway infections Dyspnoea Respiratory failure
Cardiovascular symptoms	Supraventricular arrhythmias: WPW, SVT, sick sinus syndrome or AF; In rare cases, cardiomyopathy
Gastrointestinal symptoms	Incontinence Stool urgency Diarrhoea Abdominal discomfort Cramps Early satiety Macroglossia Dysarthria Dysphagia
Urinary tract symptoms	Urinary urge incontinence Lower urinary tract symptoms
Vascular and central nervous system involvement	Dilatative arteriopathy Aneurysms Ischaemic stroke Lacunar encephalopathy Subarachnoid haemorrhage Aortic stiffness

AF — atrial fibrillation; ALT — alanine transaminase; AST — aspartate aminotransferase; CK — creatine kinase; LDH — lactate dehydrogenase; LOPD — late onset Pompe Disease; SVT — supraventricular tachycardia; WPW — Wolff-Parkinson-White syndrome

to underline the importance of testing for LOPD also those patients presenting with pulmonary or cardiac symptoms.

Material and methods

We have searched PubMed for relevant manuscripts using the terms: Late Onset Pompe Disease or LOPD and cardiac; LOPD and respiratory; LOPD and gastrointestinal; LOPD Pompe and urinary, LOPD and multisystem, LOPD and

multidisciplinary. Selected studies and also reviews in this area were assessed for further relevant citations. The reference lists of selected studies were searched for additional publications.

Neuromuscular symptoms

LOPD presents with slowly progressive limb-girdle muscle weakness in 78–95% of patients [15–18]. Muscle fatigue, exercise intolerance, decreased mobility, axial muscle weakness and myalgia are also frequently reported [1, 19–21].

Weakness may be preceded by myalgia [21]. Some patients complain of muscle cramps [22]. Even though muscle weakness progresses slowly, in the natural course of the disease it can lead to wheelchair dependence [17]. The distribution of muscle weakness varies, but most commonly it first involves the proximal muscles of the lower limbs and axial muscles, followed by the upper extremities and respiratory muscles (Tab. 1) [7].

Given the need for early diagnosis and treatment, a low threshold for screening for LOPD is crucial in patients with unclassified limb-girdle muscle weakness and/or with asymptomatic hyperCKemia [5, 10, 15, 19, 20, 23]. In the Polish population, we have performed screening for LOPD in a cohort of patients with limb-girdle muscle weakness and/or persistent hyperCKemia, confirming the diagnosis in 3% of patients. The reported rate is thus consistent with neighbouring European countries, where it has been reported as 2.4–4.2% [10, 15, 23].

Skeletal symptoms

Secondary to progressive muscle weakness, patients with Pompe Disease often develop spinal abnormalities, mostly scoliosis but also kyphosis and lumbar hyperlordosis, rigid spine syndrome (RSS), and also osteoporosis with the risk of bone and vertebral fractures [16, 24–29].

According to the international Pompe registry, scoliosis is found in 33% of patients with LOPD [25]. It is more common in patients who experience disease onset as children than it is in those with onset as adults. In some cases, surgical treatment is necessary to maintain sitting position and improve pulmonary function [24, 30]. Also, scoliosis has been found to occur in 62.5% of patients with Pompe Disease requiring a wheelchair and led to reduced pulmonary function [25].

Rigid spine syndrome is a limitation of the neck and trunk movements that causes postural abnormalities and increases the risk of respiratory insufficiency [31]. In most patients, severe axial muscle weakness is accompanied by mild to moderate extremity muscle weakness [16, 26]. In patients with RSS, Pompe Disease should be considered in a differential diagnosis [27, 32].

A Dutch study by van Berg et al. [29] showed that 67% of patients with Pompe Disease have decreased bone mineral density (BMD) and consequently are at higher risk of bone fractures due to osteoporosis. The authors suggested regular screening of BMD in children, patients who develop muscle weakness, and those who are wheelchair dependent and also with respiratory insufficiency.

Additionally, a study by Bertoldo et al. [33] reported a high prevalence of asymptomatic vertebral fractures in patients with LOPD even without significant deterioration of BMD (77% of 22 patients). The fractures were not related to trauma. This shows the need for routine screening for vertebral fractures in LOPD patients.

Respiratory symptoms

LOPD frequently presents with respiratory symptoms. Respiratory insufficiency may precede limb-girdle muscle weakness [16]. It has been described as the second most frequent initial symptom of the disease in 11–13% of patients [18, 34]. Respiratory problems have been reported in 33–60% of patients at diagnosis [15, 34]. In the study by van der Beek et al. [35], respiratory involvement was reported in 79% of adult patients and in 59% of children, with evident diaphragmatic involvement observed in 38% of those examined. In general, as the disease progresses, 29–72.2% of LOPD patients will need respiratory support [36–38].

Nocturnal hypoventilation leads to early sleep disruptions, excessive daytime fatigue and sleepiness, nocturnal dyspnoea, orthopnoea, wheezing and morning headache [39–41]. Also, respiratory muscle weakness impairs the coughing process, and therefore patients are prone to develop recurrent pulmonary infections with prolonged recovery periods [39]. Due to diaphragmatic involvement, dyspnoea is exacerbated in the supine position. Some patients may even be unable to maintain a supine position without ventilatory support [35, 39].

In most cases, symptoms progress slowly and patients adapt to the increasing pulmonary restriction [26]. Therefore, pulmonary infection can lead to decompensation and respiratory failure that mimics an acute event [42]. In most LOPD patients, respiratory failure is the main cause of death [21, 43]. Diaphragmatic insufficiency can be considered to be a hallmark of LOPD even early in the course of the disease [44, 45]. In the DIPPER screening study, performed to establish the incidence of LOPD disease in patients with paralysis of the diaphragm of unknown origin, 16.8% of patients were diagnosed with Pompe Disease. This underlines the need for screening for GAA deficiency in patients who initially present with pulmonary symptoms only, including diaphragm weakness [45]. It is indicated in every patient with unexplained respiratory symptoms requiring mechanical ventilation, especially when CK activity is elevated.

Spirometry with evaluation of forced vital capacity (FVC) in sitting and supine positions aids in diagnosing diaphragmatic weakness. Sitting FVC may still be normal, but a decrease of FVC > 10% in the supine position is considered significant [46, 47]. In LOPD, the FVC drop is usually more than 25% [7]. Maximal inspiratory pressure (MIP), sniff nasal inspiratory pressure (SNIP), maximal expiratory pressure (MEP), and peak cough flow (PCF) can also be useful parameters in LOPD [39]. Ultrasound testing can aid in the evaluation of diaphragm weakness [48].

Treatment with ERT prevents deterioration of respiratory function. A meta-analysis by Schoser et al. [12] shows a relative difference between treated and non-treated patients which increased over time — from 4.5% FVC after 12 months to 6% FVC after four years. LOPD patients may also benefit from inspiratory muscle training. When performed frequently and regularly, this can stabilise and/or slow down the deterioration of diaphragm weakness [49].

In addition to the involvement of respiratory muscles, glycogen may also accumulate in the airway's smooth muscles [50–52]. As a result, it can affect the trachea, bronchi and bronchioles, causing bronchomalacia and tracheomalacia and contributing to the need for mechanical ventilation [52–54]. Bronchoscopy should be considered in LOPD patients with progressive respiratory dysfunction preceding mechanical ventilation [52].

Cardiovascular symptoms

Although hypertrophic cardiomyopathy is an early, classic symptom in patients with IOPD, in LOPD by contrast it is rare [55]. There have only been a handful of case reports of hypertrophic cardiomyopathy in adults with Pompe Disease [36, 56, 57]. Cardiomyopathy improves with ERT [36]. A cardiovascular magnetic resonance study of LOPD reported only mild and non-specific cardiac abnormalities in a small group of patients [58].

The presence of rhythm disturbances varies greatly in different groups, from 2% up to 29.5% [16, 37]. Therefore, it is important to provide regular cardiac care to LOPD patients. Reported cardiac arrhythmias increase the risk of sudden death in LOPD [59]. There have been reports of supraventricular arrhythmias, such as Wolff–Parkinson–White syndrome (WPW), supraventricular tachycardia (SVT), sick sinus syndrome and atrial fibrillation [7, 37, 60–63]. WPW has been associated both with IOPD and LOPD, and is probably caused by the disruption of the annulus fibrosus [60, 63]. A short PR interval on ECG has been described in 8–10% of LOPD patients [21, 63]. Heart rhythm disorders with CKemia can precede neuromuscular symptoms [21].

Also, in 3% of the patients in a French LOPD cohort, atrioventricular blocks requiring pacemaker implantation were reported. It is important to remember that even though ERT improves cardiac function in patients with Pompe Disease, it does not seem to be effective in preventing arrhythmias [64].

Patients with LOPD require cardiac follow-up with electrocardiography, 24-hour Holter monitoring and also echocardiography, due to the potentially life-threatening complications [55, 64].

Cardiac involvement occurs also in other lysosomal storage disorders (Tab. 2).

Gastrointestinal symptoms

Symptoms from the gastrointestinal (GI) track are not life threatening, but they can affect quality of life (QoL) and tend to be underdiagnosed [65, 66].

Table 2. Cardiac manifestations in various lysosomal storage disorders

Condition (OMIM#, gene mutation, transmission mode)	Cardiac manifestations	Most common manifestation
Late Onset Pompe Disease (#232300, AR)	Supraventricular arrhythmias: WPW, SVT, sick sinus syndrome, AF; valvular heart disease. In rare cases, cardiomyopathy	Skeletal muscle weakness, hyperCKemia, respiratory insufficiency with diaphragm involvement
Danon Disease [93–98] (#300257, X-linked)	Cardiomyopathy, ventricular preexcitation, arrhythmias such as WPW, valvular heart disease, heart failure, or sudden cardiac death	Mental retardation, skeletal myopathy, hyperCKemia, cardiomyopathy
Anderson-Fabry Disease [95, 99–101] (#301500, X-linked)	Cardiomyopathy, heart failure, arrhythmias (short PR interval, bundle branch block, progressive AV conduction abnormalities), valvular heart disease — rarely haemodynamically significant, arterial hypertension	Angiokeratosis and corneal opacities, acroparesthesias, cardiac manifestations, gastrointestinal problems, renal involvement including renal failure, transient ischaemic attacks, recurrent strokes
Mucopolysaccharidoses [95, 99, 102–104] (MPS I: Hurler #607014, AR; MPS I: Scheie #607016, AR; MPS II: Hunter #309900, X-linked recessive; MPS IIIa #252900, AR; IIIb #252920, AR; MPS IVa #253000, AR; MPS VI #253200, AR)	Valvular heart disease (most commonly mitral valve involvement), cardiomyopathy, thickening of cardiac valves and large vessels, pulmonary hypertension	Accumulation of glycosaminoglycans causing cell and organ dysfunction; mental retardation, corneal clouding, growth retardation, contractures of joints, umbilical and inguinal hernias, kyphoscoliosis, hearing loss, hepatosplenomegaly
Mucopolipidoses [95, 99, 105, 106] (type II #252500, AR; type III #252600, AR)	Valvular heart disease	Mental retardation, skeletal deformities, malfunction of heart, lungs, liver and spleen
Gaucher Disease [99, 107, 108] (type 1 #230800, AR, type 2 #230900, AR, type 3 #231000, AR, subtype IIIC #231005, AR)	Rare: pulmonary hypertension, cor pulmonale, valve involvement, myocardial calcifications	Heterogenous phenotype; organomegaly, bone abnormalities, anaemia and thrombocytopenia; in some cases, progressive neurological degeneration

AF — atrial fibrillation; AV — atrioventricular; SVT — supraventricular tachycardia; WPW — Wolff–Parkinson–White syndrome

The accumulation of glycogen in smooth muscles may cause incontinence, stool urgency, diarrhoea, abdominal discomfort, cramps and early satiety [7, 60, 67, 68]. GI symptoms are quite common. For instance, in a German study, stool urgency and diarrhoea were reported in more than half of the patients [68].

Also, due to bulbar muscle weakness, lingual weakness and macroglossia, some patients may suffer from dysarthria and dysphagia. Screening for dysphagia is important in LOPD [7, 52, 69, 70]. Patients with bulbar muscle weakness are at risk of pulmonary complications [38]. Difficulties in feeding can lead to low body mass, poor weight gain and malnutrition [60, 71].

Urinary tract symptoms

Glycogen also tends to accumulate in the smooth muscles of the genitourinary tract [52, 72].

Urinary urge incontinence has been reported in several studies, with a higher prevalence compared to the general population [68, 73].

Lower urinary tract symptoms (LUTS) have been reported in the majority of patients with LOPD [73]. A weak, dribbling, intermittent stream, post-void dribbling, an inability to stop the stream, and urinary incontinence have been commonly reported [73]. The aetiology is speculated to be either glycogen

accumulation in smooth muscle cells of the bladder, or dysfunction of the autonomic nervous system and peripheral nerves [73, 74]. Urinary symptoms have a significant impact on QoL [73].

Other systems involvement

The involvement of the cerebrovascular, central and peripheral nervous systems have also been reported in LOPD. Various cerebrovascular abnormalities have been noted, with a higher incidence compared to the healthy population [7]. They may manifest as dilative arteriopathy or aneurysms and mainly involve posterior circulation, but the anterior circle can also be affected [75]. Glycogen can accumulate in the cells of vessel walls, diminishing smooth muscle tissue integrity and probably causing aneurysms or dilative arteriopathy [60, 76]. Patients need to be closely monitored to prevent rupture of the aneurysm. Restrictive arteriopathy has also been described [77]. Cases of stroke caused by intracranial aneurysms or arteriopathy [76, 78–80], and subarachnoid haemorrhage, have also been reported [81]. Vascular complications such as stroke may even be a presenting symptom of LOPD [78].

The involvement of the aorta, iliac arteries, renal arteries, and also cervical arteries has been reported [7, 82]. Accumulation of glycogen in the aorta may lead to aortic stiffness, causing hypertension [83].

Laboratory parameters

Most LOPD patients have mildly elevated serum CK level (1,000–1,500 U/L) [7, 20, 84]. In a review by Winkel et al. [18], over 90% of cases presented with elevated CK, LDH, AST and ALT.

Persistent CK elevation, more than 1.5× upper limit of normal, even in an asymptomatic person, should therefore raise a suspicion of Pompe Disease [10, 85].

Diagnosis

The recommended first step for the diagnosis of Pompe Disease is a test of the GAA activity. This is currently recommended to take the form of a screening test in patients with moderate CKemia, limb-girdle weakness, rigid spine syndrome, or diaphragm weakness, unless a clear alternative diagnosis can be made [15, 86, 87]. The evaluation of the GAA activity is usually performed from a dried blood spot sample. If the result is below the reference range, DNA testing may be performed from the same blood sample, where consented to. The detection of two mutations in the GAA gene confirms a Pompe diagnosis. Alternatively, GAA activity assessment in lymphocytes or in fibroblasts can be performed as a confirmatory test [9, 11].

Generally, DNA analysis is performed with PCR reactions and subsequent Sanger sequencing of all GAA coding exons. Also, an exon-flanking RT-PCR can be used to detect novel variants [88, 89]. Some mutations have been reported more frequently in different populations and locations. For example, mutation c.32–13T > G is very frequently reported in the Polish population as a heterozygous composition with missense or frameshift mutation on the other allele [10, 42]. This mutation is by far the most common in the Pompe registry, which consists mostly of Caucasians [86].

Over 400 genetic variants of Pompe Disease have been noted in the 'Pompe Disease GAA variant database' (<http://www.pompevariantdatabase.nl/>), which allows the prediction of a patient's phenotype after identifying disease variants of both alleles [90].

Conclusions

Pompe Disease is classified as a metabolic myopathy, but can manifest with various symptoms. Due to its unspecific phenotype and low prevalence, the time from onset to diagnosis remains a cause for concern [18, 91, 92]. Greater awareness of LOPD and a multidisciplinary approach to patients are required.

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