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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

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	Dilative 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
Mucolipidoses [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 rapture 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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References

1. van der Ploeg AT, Reuser AJJ. Pompe's disease. Lancet. 2008; 372(9646): 1342–1353, doi: 10.1016/s0140-6736(08)61555-x, indexed in Pubmed: 18929906.
2. Tarnopolsky M, Katzberg H, Petrof BJ, et al. Pompe disease: diagnosis and management. Evidence-based guidelines from a canadian expert panel. Can J Neurol Sci. 2016; 43(4): 472–485, doi: 10.1017/cjn.2016.37, indexed in Pubmed: 27055517.
3. Pompe JC. Over idiopathische hypertrophie van het hart. Ned Tijdshr Geneeskd. 1932; 76: 304–312.
4. Bay LB, Denzler I, Durand C, et al. Infantile-onset pompe disease: diagnosis and management. Arch Argent Pediatr. 2019; 117(4): 271–278, doi: 10.5546/aap.2019.eng.271, indexed in Pubmed: 31339275.
5. Gutiérrez-Rivas E, Bautista J, Vílchez JJ, et al. Targeted screening for the detection of Pompe disease in patients with unclassified limb--girdle muscular dystrophy or asymptomatic hyperCKemia using dried blood: a spanish cohort. Neuromuscul Disord. 2015; 25(7): 548–553, doi: 10.1016/j.nmd.2015.04.008, indexed in Pubmed: 25998610.
6. Palmio J, Auranen M, Kiuru-Enari S, et al. Screening for late-onset Pompe disease in Finland. Neuromuscul Disord. 2014; 24(11): 982–985, doi: 10.1016/j.nmd.2014.06.438, indexed in Pubmed: 25047669.
7. Toscano A, Rodolico C, Musumeci O. Multisystem late onset Pompe disease (LOPD): an update on clinical aspects. Ann Transl Med. 2019; 7(13): 284, doi: 10.21037/atm.2019.07.24, indexed in Pubmed: 31392196.
8. Kishnani PS, Steiner RD, Bali D, et al. Pompe disease diagnosis and management guideline. Genet Med. 2006; 8(5): 267–288, doi: 10.1097/01.gim.0000218152.87434.f3, indexed in Pubmed: 16702877.
9. Llerena Junior JC, Nascimento OJm, Oliveira AS, et al. Guidelines for the diagnosis, treatment and clinical monitoring of patients with juvenile and adult Pompe disease. Arq Neuropsiquiatr. 2016; 74(2): 166–176, doi: 10.1590/0004-282X20150194, indexed in Pubmed: 26690841.
10. Jastrzębska A, Potulska-Chromik A, Łusakowska A, et al. Screening for late-onset Pompe disease in Poland. Acta Neurol Scand. 2019; 140(4): 239–243, doi: 10.1111/ane.13133, indexed in Pubmed: 31125121.
11. Chien YH, Hwu WL, Lee NC. Pompe disease: early diagnosis and early treatment make a difference. Pediatr Neonatol. 2013; 54(4): 219–227, doi: 10.1016/j.pedneo.2013.03.009, indexed in Pubmed: 23632029.
12. Schoser B, Stewart A, Kanters S, et al. Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis. J Neurol. 2017; 264(4): 621–630, doi: 10.1007/s00415-016-8219-8, indexed in Pubmed: 27372449.
13. Harlaar L, Hogrel JY, Perniconi B, et al. Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease. Neurology. 2019; 93(19): e1756–e1767, doi: 10.1212/WNL.0000000000008441, indexed in Pubmed: 31619483.
14. van der Ploeg AT, Clemens PR, Corzo D, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med. 2010; 362(15): 1396–1406, doi: 10.1056/NEJMoa0909859, indexed in Pubmed: 20393176.
15. Lukacs Z, Nieves Cobos P, Wenninger S, et al. Prevalence of Pompe disease in 3,076 patients with hyperCKemia and limb-girdle mu-

scular weakness. Neurology. 2016; 87(3): 295–298, doi: 10.1212/WNL.0000000000002758, indexed in Pubmed: 27170567.
16. Schüller A, Wenninger S, Strigl-Pill N, et al. Toward deconstructing the phenotype of late-onset Pompe disease. Am J Med Genet C Semin Med Genet. 2012; 160C(1): 80–88, doi: 10.1002/ajmg.c.31322, indexed in Pubmed: 22253010.
17. Hagemans MLC, Winkel LPF, Van Doorn PA, et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. Brain. 2005; 128(Pt 3): 671–677, doi: 10.1093/brain/awh384, indexed in Pubmed: 15659425.
18. Winkel LPF, Hagemans MLC, van Doorn PA, et al. The natural course of non-classic Pompe's disease; a review of 225 published cases. J Neurol. 2005; 252(8): 875–884, doi: 10.1007/s00415-005-0922-9, indexed in Pubmed: 16133732.
19. Preisler N, Lukacs Z, Vinge L, et al. Late-onset Pompe disease is prevalent in unclassified limb-girdle muscular dystrophies. Mol Genet Metab. 2013; 110(3): 287–289, doi: 10.1016/j.ymgme.2013.08.005, indexed in Pubmed: 24011652.
20. Lorenzoni PJ, Kay CS, Higashi NS, et al. Late-onset Pompe disease: what is the prevalence of limb-girdle muscular weakness presentation? Arq Neuropsiquiatr. 2018; 76(4): 247–251, doi: 10.1590/0004-282x20180018, indexed in Pubmed: 29742245.
21. Müller-Felber W, Horvath R, Gempel K, et al. Late onset Pompe disease: clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. Neuromuscul Disord. 2007; 17(9-10): 698–706, doi: 10.1016/j.nmd.2007.06.002, indexed in Pubmed: 17643989.
22. Chu YP, Sheng B, Lau KK, et al. Clinical manifestation of late onset Pompe disease patients in Hong Kong. Neuromuscul Disord. 2016; 26(12): 873–879, doi: 10.1016/j.nmd.2016.09.004, indexed in Pubmed: 27692865.
23. Ünver O, Hacıfazlıoğlu NE, Karatoprak E, et al. The frequency of late-onset Pompe disease in pediatric patients with limb-girdle muscle weakness and nonspecific hyperCKemia: A multicenter study. Neuromuscul Disord. 2016; 26(11): 796–800, doi: 10.1016/j.nmd.2016.09.001, indexed in Pubmed: 27666774.
24. Haaker G, Forst J, Forst R, et al. Orthopedic management of patients with Pompe disease: a retrospective case series of 8 patients. ScientificWorldJournal. 2014; 2014: 963861, doi: 10.1155/2014/963861, indexed in Pubmed: 24523658.
25. Roberts M, Kishnani PS, van der Ploeg AT, et al. The prevalence and impact of scoliosis in Pompe disease: lessons learned from the Pompe Registry. Mol Genet Metab. 2011; 104(4): 574–582, doi: 10.1016/j.ymgme.2011.08.011, indexed in Pubmed: 21930409.
26. Kostera-Pruszczyk A, Opuchlik A, Lugowska A, et al. Juvenile onset acid maltase deficiency presenting as a rigid spine syndrome. Neuromuscul Disord. 2006; 16(4): 282–285, doi: 10.1016/j.nmd.2006.02.001, indexed in Pubmed: 16531044.
27. Laforêt P, Doppler V, Caillaud C, et al. Rigid spine syndrome revealing late-onset Pompe disease. Neuromuscul Disord. 2010; 20(2): 128–130, doi: 10.1016/j.nmd.2009.11.006, indexed in Pubmed: 20005713.
28. Bertoldo F, Zappini F, Brigo M, et al. Prevalence of asymptomatic vertebral fractures in late-onset Pompe disease. J Clin Endocrinol Metab. 2015; 100(2): 401–406, doi: 10.1210/jc.2014-2763, indexed in Pubmed: 25396301.
29. van den Berg LEM, Zandbergen AA, van Capelle CI, et al. Low bone mass in Pompe disease: muscular strength as a predictor of bone mineral density. Bone. 2010; 47(3): 643–649, doi: 10.1016/j.bone.2010.06.021, indexed in Pubmed: 20601298.
30. Kawakami K, Kawakami N, Nohara A, et al. Spinal fusion as a viable treatment option for scoliosis management in Pompe disease: a postoperative 3-year follow-up. Eur Spine J. 2016; 25 Suppl 1: 140–146, doi: 10.1007/s00586-015-4249-7, indexed in Pubmed: 26411350.
31. Dubowitz V. Rigid spine syndrome: a muscle syndrome in search of a name. Proc R Soc Med. 1973; 66(3): 219–220, indexed in Pubmed: 4697975.
32. Fadic R, Waclawik AJ, Brooks BR, et al. The rigid spine syndrome due to acid maltase deficiency. Muscle Nerve. 1997; 20(3): 364–366, doi: 10.1002/(SICI)1097-4598(199703)20:3<364::AID-MUS16>3.0.CO;2-0, indexed in Pubmed: 9052818.
33. Bertoldo F, Zappini F, Brigo M, et al. Prevalence of asymptomatic vertebral fractures in late-onset Pompe disease. J Clin Endocrinol Metab. 2015; 100(2): 401–406, doi: 10.1210/jc.2014-2763, indexed in Pubmed: 25396301.
34. Vanherpe P, Fieuws S, D'Hondt A, et al. Late-onset Pompe disease (LOPD) in Belgium: clinical characteristics and outcome measures. Orphanet J Rare Dis. 2020; 15(1): 83, doi: 10.1186/s13023-020-01353-4, indexed in Pubmed: 32248831.
35. van der Beek NA, van Capelle CI, van der Velden-van Etten KI, et al. Rate of progression and predictive factors for pulmonary outcome in children and adults with Pompe disease. Mol Genet Metab. 2011; 104(1-2): 129–136, doi: 10.1016/j.ymgme.2011.06.012, indexed in Pubmed: 21763167.
36. Alandy-Dy J, Wencel M, Hall K, et al. Variable clinical features and genotype-phenotype correlations in 18 patients with late-onset Pompe disease. Ann Transl Med. 2019; 7(13): 276, doi: 10.21037/atm.2019.06.48, indexed in Pubmed: 31392188.
37. Soliman OII, van der Beek NA, van Doorn PA, et al. Cardiac involvement in adults with Pompe disease. J Intern Med. 2008; 264(4): 333–339, doi: 10.1111/j.1365-2796.2008.01966.x, indexed in Pubmed: 18397245.
38. van der Beek NA, de Vries JM, Hagemans MLC, et al. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. Orphanet J Rare Dis. 2012; 7: 88, doi: 10.1186/1750-1172-7-88, indexed in Pubmed: 23147228.
39. Boentert M, Prigent H, Várdi K, et al. Practical recommendations for diagnosis and management of respiratory muscle weakness in late-onset Pompe disease. Int J Mol Sci. 2016; 17(10): 1735, doi: 10.3390/ijms17101735, indexed in Pubmed: 27763517.
40. Boentert M, Karabul N, Wenninger S, et al. Sleep-related symptoms and sleep-disordered breathing in adult Pompe disease. Eur J Neurol. 2015; 22(2): 369–376, e27, doi: 10.1111/ene.12582, indexed in Pubmed: 25367349.
41. De Vito EL, Arce SC, Monteiro SG, et al. Central drive and ventilatory failure in late-onset Pompe disease: at the gates of a new phenotype. Neuromuscul Disord. 2019; 29(6): 444–447, doi: 10.1016/j.nmd.2019.03.008, indexed in Pubmed: 31130377.
42. Witkowski G, Konopko M, Rola R, et al. Enzymatic replacement therapy in patients with late-onset Pompe disease - 6-Year follow up. Neurol Neurochir Pol. 2018; 52(4): 465–469, doi: 10.1016/j.pjnns.2018.05.002, indexed in Pubmed: 29803406.
43. Herzog A, Hartung R, Reuser AJJ, et al. A cross-sectional single-centre study on the spectrum of Pompe disease, German patients: molecular analysis of the GAA gene, manifestation and genotype-phenotype correlations. Orphanet J Rare Dis. 2012; 7: 35, doi: 10.1186/1750-1172-7-35, indexed in Pubmed: 22676651.
44. Gaeta M, Musumeci O, Mondello S, et al. Clinical and pathophysiological clues of respiratory dysfunction in late-onset Pompe disease:

New insights from a comparative study by MRI and respiratory function assessment. Neuromuscul Disord. 2015; 25(11): 852–858, doi: 10.1016/j.nmd.2015.09.003, indexed in Pubmed: 26410244.
45. Guimarães MJ, Winck JC, Conde B, et al. Prevalence of late-onset pompe disease in Portuguese patients with diaphragmatic paralysis - DIPPER study. Rev Port Pneumol (2006). 2017; 23(4): 208–215, doi: 10.1016/j.rppnen.2017.02.004, indexed in Pubmed: 28499810.
46. Berger KI, Chan Y, Rom WN, et al. Progression from respiratory dysfunction to failure in late-onset Pompe disease. Neuromuscul Disord. 2016; 26(8): 481–489, doi: 10.1016/j.nmd.2016.05.018, indexed in Pubmed: 27297666.
47. American Association of Neuromuscular & Electrodiagnostic Medicine. Diagnostic criteria for late-onset (childhood and adult) Pompe disease. Muscle Nerve. 2009; 40(1): 149–160, doi: 10.1002/mus.21393, indexed in Pubmed: 19533647.
48. Spiesshoefer J, Henke C, Kabitz HJ, et al. The nature of respiratory muscle weakness in patients with late-onset Pompe disease. Neuromuscul Disord. 2019; 29(8): 618–627, doi: 10.1016/j.nmd.2019.06.011, indexed in Pubmed: 31327549.
49. Wenninger S, Greckl E, Babačić H, et al. Safety and efficacy of short- and long-term inspiratory muscle training in late-onset Pompe disease (LOPD): a pilot study. J Neurol. 2019; 266(1): 133–147, doi: 10.1007/s00415-018-9112-4, indexed in Pubmed: 30430231.
50. McCall AL, ElMallah MK. Macroglossia, motor neuron pathology, and airway malacia contribute to respiratory insufficiency in pompe disease: a commentary on molecular pathways and respiratory involvement in lysosomal storage diseases. Int J Mol Sci. 2019; 20(3): 751, doi: 10.3390/ijms20030751, indexed in Pubmed: 30754627.
51. Pena LDM, Proia AD, Kishnani PS. Postmortem findings and clinical correlates in individuals with infantile-onset pompe disease. JIMD Rep. 2015; 23: 45–54, doi: 10.1007/8904_2015_426, indexed in Pubmed: 25763511.
52. McCall AL, Salemi J, Bhanap P, et al. The impact of Pompe disease on smooth muscle: a review. J Smooth Muscle Res. 2018; 54(0): 100–118, doi: 10.1540/jsmr.54.100, indexed in Pubmed: 30787211.
53. Brenn BR, Theroux MT, Shah SA, et al. Critical airway stenosis in an adolescent male with pompe disease and thoracic lordosis: a case report. A A Case Rep. 2017; 9(7): 199–203.
54. Yang CF, Niu DM, Jeng MJ, et al. Late-onset Pompe disease with left-sided bronchomalacia. Respir Care. 2015; 60(2): e26–e29, doi: 10.4187/respcare.03419, indexed in Pubmed: 25316892.
55. Herbert M, Cope H, Li JS, et al. Severe cardiac involvement is rare in patients with late-onset pompe disease and the common c.-32-13T>G variant: implications for newborn screening. J Pediatr. 2018; 198: 308–312, doi: 10.1016/j.jpeds.2018.02.007, indexed in Pubmed: 29627187.
56. Mori M, Bailey LA, Estrada J, et al. Severe cardiomyopathy as the isolated presenting feature in an adult with late-onset pompe disease: a case report. JIMD Rep. 2017; 31: 79–83, doi: 10.1007/8904_2016_563, indexed in Pubmed: 27142047.
57. Lee DH, Qiu WJ, Lee J, et al. Hypertrophic cardiomyopathy in pompe disease is not limited to the classic infantile-onset phenotype. JIMD Rep. 2014; 17: 71–75, doi: 10.1007/8904_2014_339, indexed in Pubmed: 25213570.
58. Boentert M, Florian A, Dräger B, et al. Pattern and prognostic value of cardiac involvement in patients with late-onset pompe disease: a comprehensive cardiovascular magnetic resonance approach. J Cardiovasc Magn Reson. 2016; 18(1): 91, doi: 10.1186/s12968-016-0311-9, indexed in Pubmed: 27931223.
59. Tabarki B, Mahdhaoui A, Yacoub M, et al. [Familial hypertrophic cardiomyopathy associated with Wolff-Parkinson-White syndrome revealing type II glycogenosis]. Arch Pediatr. 2002; 9(7): 697–700, doi: 10.1016/s0929-693x(01)00968-x, indexed in Pubmed: 12162158.
60. Chan J, Desai AK, Kazi ZB, et al. The emerging phenotype of late-onset Pompe disease: a systematic literature review. Mol Genet Metab. 2017; 120(3): 163–172, doi: 10.1016/j.ymgme.2016.12.004, indexed in Pubmed: 28185884.
61. Francesconi M, Auff E. Cardiac arrhythmias and the adult form of type II glycogenosis. N Engl J Med. 1982; 306(15): 937–938, doi: 10.1056/NEJM198204153061515, indexed in Pubmed: 6950223.
62. Francesconi M, Auff E, Ursin C, et al. [WPW syndrome combined with AV block 2 in an adult with glycogenosis (Type II)]. Wien Klin Wochenschr. 1982; 94(15): 401–404, indexed in Pubmed: 6959422.
63. Forsha D, Li JS, Smith PB, et al. Late-Onset Treatment Study Investigators. Cardiovascular abnormalities in late-onset Pompe disease and response to enzyme replacement therapy. Genet Med. 2011; 13(7): 625–631, doi: 10.1097/GIM.0b013e3182142966, indexed in Pubmed: 21543987.
64. Sacconi S, Wahbi K, Theodore G, et al. Atrio-ventricular block requiring pacemaker in patients with late onset Pompe disease. Neuromuscul Disord. 2014; 24(7): 648–650, doi: 10.1016/j.nmd.2014.04.005, indexed in Pubmed: 24844452.
65. Bernstein DL, Bialer MG, Mehta L, et al. Pompe disease: dramatic improvement in gastrointestinal function following enzyme replacement therapy. A report of three later-onset patients. Mol Genet Metab. 2010; 101(2-3): 130–133, doi: 10.1016/j.ymgme.2010.06.003, indexed in Pubmed: 20638881.
66. Korlimarla A, Lim JA, McIntosh P, et al. New insights into gastrointestinal involvement in late-onset Pompe disease: lessons learned from bench and bedside. J Clin Med. 2021; 10(15), doi: 10.3390/jcm10153395, indexed in Pubmed: 34362174.
67. Remiche G, Herbaut AG, Ronchi D, et al. Incontinence in late-onset Pompe disease: an underdiagnosed treatable condition. Eur Neurol. 2012; 68(2): 75–78, doi: 10.1159/000338776, indexed in Pubmed: 22760201.
68. Karabul N, Skudlarek A, Berndt J, et al. Urge incontinence and gastrointestinal symptoms in adult patients with pompe disease: a cross-sectional survey. JIMD Rep. 2014; 17: 53–61, doi: 10.1007/8904_2014_334, indexed in Pubmed: 25155777.
69. Hobson-Webb LD, Jones HN, Kishnani PS. Oropharyngeal dysphagia may occur in late-onset Pompe disease, implicating bulbar muscle involvement. Neuromuscul Disord. 2013; 23(4): 319–323, doi: 10.1016/j.nmd.2012.12.003, indexed in Pubmed: 23332114.
70. Dubrovsky A, Corderi J, Lin M, et al. Expanding the phenotype of late-onset Pompe disease: tongue weakness: a new clinical observation. Muscle Nerve. 2011; 44(6): 897–901, doi: 10.1002/mus.22202, indexed in Pubmed: 21953123.
71. Cupler EJ, Berger KI, Leshner RT, et al. AANEM Consensus Committee on Late-onset Pompe Disease. Consensus treatment recommendations for late-onset Pompe disease. Muscle Nerve. 2012; 45(3): 319–333, doi: 10.1002/mus.22329, indexed in Pubmed: 22173792.
72. van der Walt JD, Swash M, Leake J, et al. The pattern of involvement of adult-onset acid maltase deficiency at autopsy. Muscle Nerve. 1987; 10(3): 272–281, doi: 10.1002/mus.880100311, indexed in Pubmed: 2951596.
73. McNamara ER, Austin S, Case L, et al. Expanding our understanding of lower urinary tract symptoms and incontinence in adults with pompe disease. JIMD Rep. 2015; 20: 5–10, doi: 10.1007/8904_2014_381, indexed in Pubmed: 25614307.

74. Fidziańska A, Ługowska A, Tylki-Szymańska A. Late form of Pompe disease with glycogen storage in peripheral nerves axons. J Neurol Sci. 2011; 301(1-2): 59–62, doi: 10.1016/j.jns.2010.10.031, indexed in Pubmed: 21109266.
75. Pichiecchio A, Sacco S, De Filippi P, et al. Late-onset Pompe disease: a genetic-radiological correlation on cerebral vascular anomalies. J Neurol. 2017; 264(10): 2110–2118, doi: 10.1007/s00415-017-8601-1, indexed in Pubmed: 28856460.
76. Kretzschmar HA, Wagner H, Hübner G, et al. Aneurysms and vacuolar degeneration of cerebral arteries in late-onset acid maltase deficiency. J Neurol Sci. 1990; 98(2-3): 169–183, doi: 10.1016/0022-510x(90)90258-o, indexed in Pubmed: 2243227.
77. Malhotra K, Carrington DC, Liebeskind DS. Restrictive arteriopathy in late-onset Pompe disease: case report and review of the literature. J Stroke Cerebrovasc Dis. 2017; 26(8): e172–e175, doi: 10.1016/j.jstrokecerebrovasdis.2017.05.032, indexed in Pubmed: 28647415.
78. Laforêt P, Petiot P, Nicolino M, et al. Dilative arteriopathy and basilar artery dolichoectasia complicating late-onset Pompe disease. Neurology. 2008; 70(22): 2063–2066, doi: 10.1212/01.wnl.0000313367.09469.13, indexed in Pubmed: 18505979.
79. Matsuoka Y, Senda Y, Hirayama M, et al. Late-onset acid maltase deficiency associated with intracranial aneurysm. J Neurol. 1988; 235(6): 371–373, doi: 10.1007/BF00314237, indexed in Pubmed: 3139844.
80. Huded V, Bohra V, Prajapati J, et al. Stroke in young-dilative arteriopathy: a clue to late-onset Pompe's disease? J Stroke Cerebrovasc Dis. 2016; 25(4): e50–e52, doi: 10.1016/j.jstrokecerebrovasdis.2016.01.021, indexed in Pubmed: 26853144.
81. Peric S, Fumic K, Bilic K, et al. Rupture of the middle cerebral artery aneurysm as a presenting symptom of late-onset Pompe disease in an adult with a novel GAA gene mutation. Acta Neurol Belg. 2014; 114(2): 165–166, doi: 10.1007/s13760-013-0265-8, indexed in Pubmed: 24338761.
82. Quenardelle V, Bataillard M, Bazin D, et al. Pompe disease presenting as an isolated generalized dilative arteriopathy with repeated brain and kidney infarcts. J Neurol. 2015; 262(2): 473–475, doi: 10.1007/s00415-014-7582-6, indexed in Pubmed: 25451853.
83. Nemes A, Soliman OII, Geleijnse ML, et al. Increased aortic stiffness in glycogenosis type 2 (Pompe's disease). Int J Cardiol. 2007; 120(1): 138–141, doi: 10.1016/j.ijcard.2006.07.215, indexed in Pubmed: 17084921.
84. Vissing J, Lukacs Z, Straub V. Diagnosis of Pompe disease: muscle biopsy vs blood-based assays. JAMA Neurol. 2013; 70(7): 923–927, doi: 10.1001/2013.jamaneurol.486, indexed in Pubmed: 23649721.
85. Toscano A, Montagnese F, Musumeci O. Early is better? A new algorithm for early diagnosis in late onset Pompe disease (LOPD). Acta Myol. 2013; 32(2): 78–81, indexed in Pubmed: 24399862.
86. Reuser AJJ, van der Ploeg AT, Chien YH, et al. GAA variants and phenotypes among 1,079 patients with Pompe disease: Data from the Pompe Registry. Hum Mutat. 2019; 40(11): 2146–2164, doi: 10.1002/humu.23878, indexed in Pubmed: 31342611.
87. Musumeci O, la Marca G, Spada M, et al. Italian GSD II group. LOPED study: looking for an early diagnosis in a late-onset Pompe disease high-risk population. J Neurol Neurosurg Psychiatry. 2016; 87(1): 5–11, doi: 10.1136/jnnp-2014-310164, indexed in Pubmed: 25783438.
88. In ,t Groen SLM, de Faria DOS, Iuliano A, et al. Novel variants and mosaicism in Pompe disease identified by extended analyses of patients with an incomplete DNA diagnosis. Mol Ther Methods Clin Dev. 2020; 17: 337–348, doi: 10.1016/j.omtm.2019.12.016, indexed in Pubmed: 32071926.
89. Burton BK, Kronn DF, Hwu WL, et al. Pompe Disease Newborn Screening Working Group. The initial evaluation of patients after positive newborn screening: recommended algorithms leading to a confirmed diagnosis of Pompe disease. Pediatrics. 2017; 140(Suppl 1): S14–S23, doi: 10.1542/peds.2016-0280D, indexed in Pubmed: 29162674.
90. Niño MY, In ,t Groen SLM, Bergsma AJ, et al. Extension of the Pompe mutation database by linking disease-associated variants to clinical severity. Hum Mutat. 2019; 40(11): 1954–1967, doi: 10.1002/humu.23854, indexed in Pubmed: 31254424.
91. Semplicini C, Letard P, De Antonio M, et al. French Pompe Study Group. Late-onset Pompe disease in France: molecular features and epidemiology from a nationwide study. J Inherit Metab Dis. 2018; 41(6): 937–946, doi: 10.1007/s10545-018-0243-7, indexed in Pubmed: 30155607.
92. Kishnani PS, Amartino HM, Lindberg C, et al. Pompe Registry Boards of Advisors. Timing of diagnosis of patients with Pompe disease: data from the Pompe registry. Am J Med Genet A. 2013; 161A(10): 2431–2443, doi: 10.1002/ajmg.a.36110, indexed in Pubmed: 23997011.
93. Finsterer J, Stöllberger C, Maeztu C. Sudden cardiac death in neuromuscular disorders. Int J Cardiol. 2016; 203: 508–515, doi: 10.1016/j.ijcard.2015.10.176, indexed in Pubmed: 26551884.
94. D'souza RS, Levandowski C, Slavov D, et al. Danon disease: clinical features, evaluation, and management. Circ Heart Fail. 2014; 7(5): 843–849, doi: 10.1161/CIRCHEARTFAILURE.114.001105, indexed in Pubmed: 25228319.
95. Mueller P, Attenhofer Jost CH, Rohrbach M, et al. Cardiac disease in children and young adults with various lysosomal storage diseases: Comparison of echocardiographic and ECG changes among clinical groups. Int J Cardiol Heart Vessel. 2013; 2: 1–7, doi: 10.1016/j.ijchv.2013.10.002, indexed in Pubmed: 29450157.
96. Arad M, Maron BJ, Gorham JM, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. N Engl J Med. 2005; 352(4): 362–372, doi: 10.1056/NEJMoa033349, indexed in Pubmed: 15673802.
97. Arbustini E, Di Toro A, Giuliani L, et al. Cardiac phenotypes in hereditary muscle disorders: JACC state-of-the-art review. J Am Coll Cardiol. 2018; 72(20): 2485–2506, doi: 10.1016/j.jacc.2018.08.2182, indexed in Pubmed: 30442292.
98. Boucek D, Jirikowic J, Taylor M. Natural history of Danon disease. Genet Med. 2011; 13(6): 563–568, doi: 10.1097/GIM.0b013e31820ad795, indexed in Pubmed: 21415759.
99. Nair V, Belanger EC, Veinot JP. Lysosomal storage disorders affecting the heart: a review. Cardiovasc Pathol. 2019; 39: 12–24, doi: 10.1016/j.carpath.2018.11.002, indexed in Pubmed: 30594732.
100. Tuttolomondo A, Pecoraro R, Simonetta I, et al. Anderson-Fabry disease: a multiorgan disease. Curr Pharm Des. 2013; 19(33): 5974–5996, doi: 10.2174/13816128113199990352, indexed in Pubmed: 23448451.