Think of late-onset POMPE disease

Dare to diagnose...

...It is a treatable disease

Change the outlook for patients with Pompe disease

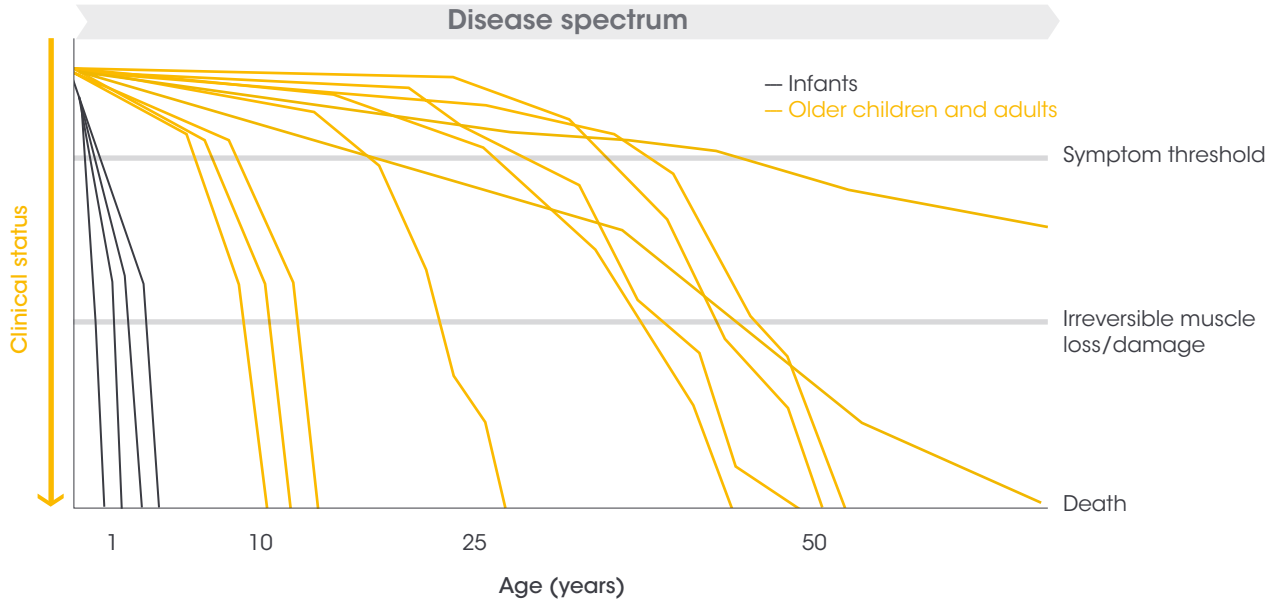
POMPE disease

SANOFI GENZYME

Pompe disease is a life-threatening, progressive neuromuscular disorder[1]

Pompe disease is caused by a deficiency of acid alpha-glucosidase (GAA) enzyme activity, which results in lysosomal glycogen accumulation in muscles and irreversible muscle damage[1]

Progressive muscular degeneration across spectrum of disease[a]



Pompe disease has a broad spectrum of clinical phenotypes and patients can present before 1 year of age (infantile-onset Pompe disease or IOPD) or after 1 year, as children and adults (late-onset Pompe disease or LOPD).[1-4]

[a]Intended to conceptually illustrate variability of disease progression; graphical depiction not based on individual patient data.

While clinical presentation and age of symptom onset is variable, patients with LOPD frequently exhibit the following signs and symptoms:

1. **Proximal/ axial weakness (LGMD*-like)**[5]
   *Limb-Girdle Muscular Dystrophy

AND /OR

2. **Restrictive respiratory insufficiency**[5]

AND /OR

3. **Asymptomatic hyperCKemia**[5]

If left undiagnosed and untreated, Pompe disease progresses with severe outcomes[3]

The median delay to definitive diagnosis for patients with LOPD can range from 6 to 13 years[6]. Without prompt clinical intervention, LOPD patients face significant risk of disability and even premature death[3,7]

Probability of wheelchair use increases, on average, 13% annually after diagnosis[3]

13% ↑

Annually after diagnosis for wheelchair use

Probability of respiratory support increases, on average, 8% annually after diagnosis[3]

8% ↑

Annually after diagnosis for respiratory support

54 years

Median age at death as reported by epidemiologic research[8]

Pompe disease is one of the few neuromuscular conditions with an availabe, disease-specific treatment[9,25]

Myozyme® (alglucosidase alfa)

-59% mortality risk

Enzyme replacement therapy (ERT) with **Myozyme®**, which replaces the deficient enzyme in Pompe disease, has been shown to **reduce risk of mortality** in patients with LOPD by **59%** compared with no ERT treatment at all[7*]

overall survival

Clinical and observational data also show a clinically relevant efficacy trend in the effect of ERT on **overall survival, motor function, and respiratory status** in patients with LOPD[7, 10-12]

Test symptomatic patients for Pompe disease. EARLY diagnosis and treatment may result in improved outcomes[5,7,9]

*Data were collected as part of an international observational study conducted between 2002 and 2011, in which patients were followed on an annual basis. Time dependent Cox's proportional hazards models were used for univariable and multivariable analyses. Overall, 283 adult patients with a median age of 48 years (range, 19 to 81 years) were included in thes tudy. After adjustment for age, sex, country of residence, and disease severity (based on wheelchair and ventilator use), ERT was positively associated with survival (hazard ratio, 0.41; 95% CI, 0.19 to 0.87).

Consider re-examining patients with unspecified limb-girdle myopathies because they could be suffering from Pompe disease

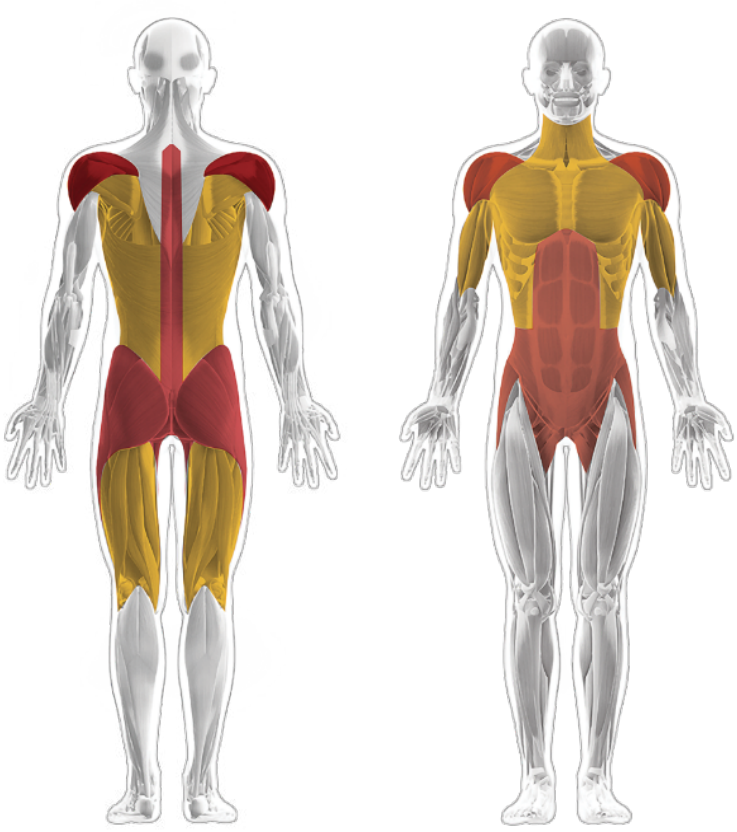
1 **Proximal/ axial weakness (LGMD*-like)[5]**

*Limb-Girdle Muscular Dystrophy

Progressive proximal muscle weakness affects the majority of late-onset patients[13]

- **> 80% of patients**
- **50%- 80% of patients**
- **< 50% of patients**

Distribution of skeletal muscle weakness in 94 adults with Pompe disease. Adapted from van der Beek.[13]



- Proximal muscles in the lower limbs are generally more severely affected than proximal muscles in the upper limbs[1]
- Trunk, paraspinal and abdominal muscles are often affected early in the course of the disease[13]

Recent studies show a high prevalence of Pompe disease in patients initially presenting with unspecified limb-girdle myopathy[14-19]

Author	Testing criteria	No. of patients tested	No. of positive Pompe diagnoses
Preisler (2013)[14]	Unclassified LGMD (**limb-girdle** muscular dystrophy)	38	3 **(8%)**
Gutiérrez-Rivas (2015) [15]	Unclassified LGMD or asymptomatic **hyperCKemia**	146*	11 **(7.5%)**
Musumeci (2016)[16]	Adult patients with isolated **limb-girdle** muscle weakness	79	1 **(1.3%)**
	Limb-girdle muscle weakness with **hyperCKemia**	427	11 **(2.6%)**
Lukacs (2016)[17]	Unselected adults with limb-girdle muscle weakness and **hyperCKemia**	2338	63 **(2.78%)**
Ünver (2016)[18]	Pediatric study with children with either **hyperCKemia** or LGMD	37*	1 **(2.7%)**
Almeida (2017)[19]	Patients presented with a phenotype of LGMD with or without **hyperCKemia**	81	4 **(4.9%)**

*LGMD alone

Consider re-examining patients with persistent hyperCKemia because they could be suffering from Pompe disease

3 Asymptomatic hyperCKemia[5]

Serum creatine kinase (CK), a biomarker of muscle damage, is usually elevated in LOPD[22]

- CK increases may be mild to moderate (e.g., 1.5 to 15 times the upper limit of normal)[22]
- CK within normal range does not necessarily rule out LOPD[22]
- Diagnostic workup of asymptomatic creatine kinase elevation[adapted from 23]:

Elevated creatine kinase (CK)
and no muscle symptoms, and normal muscle examination

↓

Repeat CK measurement ⟶ if normal stop
after 7 days, avoiding exercise in the interval

↓

CK level> 1.5 times the upper limit of normal for sex and race, ie: ⟶ if not, stop and observe
> 1.200 IU/L in a black man, > 621 IU/L in a black woman,
> 504 IU/L in a white man, > 325 IU/L in a white woman

↓

Rule out nonneuromuscular causes ⟶ if present, treat
such as: endocrine disorders, connective tissue diseases, cardiac and renal diseases, viral illness, pregnancy, celiac disease, medications (eg statins), metabolic diseases, surgery, malignancy, macro CK

↓

Electromyography, muscle biopsy and other diagnostic tests such as enzyme activity testing
- If all normal, "idiopathic hyper-CK-emia"
- If abnormal, pursue workup of neuromuscular causes
  such as: dystrophies, metabolic conditions (such as Pompe disease), congenital conditions, inflammatory conditions

Recent studies show a high prevalence of Pompe disease in patients initially presenting with hyperCKemia[15-18, 20,21,24]

Author	Testing criteria	No. of patients tested	No. of positive Pompe diagnoses
Fernandez (2006)[20]	Pauci- or asymptomatic **hyperCKemia** of unknown cause	104	4 **(3.8%)**
Spada (2013)[21]	Patients with asymptomatic unexplained **hyperCKemia**	137	3 **(2.2%)**
Gutiérrez-Rivas (2015)[15]	Unclassified LGMD or asymptomatic **hyperCKemia**	202*	5 **(2.5%)**
Musumeci (2016)[16]	Isolated **hyperCKemia**	545	5 **(0.9%)**
Lukacs (2016)[17]	Isolated **hyperCKemia** in consecutiv neuromuscular patients	738	9 **(1.2%)**
Ünver (2016)[18]	Pediatric study with children with either **hyperCKemia** or LGMD	35*	2 **(5.7%)**
Tehrani (2017)[24]	Patients with **hyperCKemia** whether or not with LGMD	93 (89 also had LGMD)	3 **(3.2%)**

*hyperCKemia alone

Include LOPD in your differential diagnoses when faced with hallmark symptoms

1

Suspect LOPD

Progressive proximal muscle weakness, with or without respiratory insufficiency or unexplained hyperCKemia, should raise suspicion of LOPD[5]

2

Test for LOPD

Test is rapid and reliable with a DBS or whole blood enzyme assay

The importance of sibling testing[5]:

When you have diagnosed one patient, it is possible that their brother(s) and/or sister(s) may have Pompe disease as well. They may or may not present with signs or symptoms or may present signs and symptoms differently to the diagnosed patient.

a

Enzyme activity testing GAA

b

Genotyping *GAA*

c

Confirmation on cultivated fibroblasts

Confirmation of a deficiency of acid a-glucosidase on a culture of skin fibroblasts is required for refund in Belgium.

To confirm Pompe disease and subsequent therapy initiation refer the patient specialized centers for neuromuscular or metabolic disorders.

CRIM ANALYSIS*
Cross-Reactive Immunologic material
Attention: Determine the CRIM status before treating Infantile Onset Pompe Disease (IOPD)

3

Treat LOPD

Unlike many other neuromuscular disorders, Pompe disease has a disease-specific treatment[9]

Myozyme® (alglucosidase alfa)

1. Hirschhorn et al., OMMBID New York, NY: McGraw-Hill; 2001. http://ommbid.mhmedical.com/content.aspx?bookid=971&sectionid=6264199 Accessed July 28 2017. **2.** Kishnani PS et al., J Pediatr. 2006; 148:671-676. **3.**Hagemans et al., Neurology. 2005; 64: 2139-2141. **4.**Hagemans et al., Neurology. 2006; 66:581-583. **5.** Toscano et al., Acta Myol. 2013; 32(2): 78-81. **6.** Kishnani et al., Am J Med Genet A. 2013; 161(10): 2431-2443. **7.** Güngör et al., Orphanet J Rare Dis. 2013; 8:49. **8.** Byrne et al., Mol Genet Metab. 2011; 103(1): 1-11. **9.** Cupler et al., Muscle Nerve. 2012; 45(3): 319-333. **10.** Strothotte, et al.; J Neurol. 2010; 257(1): 91-97. **11.** Van der Ploeg et al., N Engl J Med. 2010; 362(15): 1396-1406. **12.** European Medicines Agency Assessment Report, Myozyme. http://www.ema.europa.eu/docs/en_GB/document_library/ EPAR_-_Assessment_Report_-Variation/human/000636/WC500160105.pdf accessed Nov 14 2017. **13.** Van der Beek et al., Orphanet J Rare Dis. 2012, 7:88. **14.** Preisler N et al., Mol Genet Metab. 2013; 110(3): 287-9. **15.** Gutiérrez-Rivas et al., Neuromuscul Disord. 2015, 25(7):548-53. **16.** Musumeci O et al., J Neurol Neurosurg Psychiatr. 2016; 87(1): 5-11. **17.** Lukacs Z et al., Neurology. 2016; 87(3): 295-8. **18.** Ünver et al., Neuromuscul Disord. 2016,26(11):796-800. **19.** Almeida et al., Neuromuscul Disord. 2017,27(8):777-781. **20.** Fernandez C et al., Neurology. 2006; 66(10): 1585-7. **21.** Spada M et al., Mol Genet Metab. 2013; 109(2): 171-3. **22.** AANEM. Muscle Nerve. 2009; 40: 149-160. **23.** Moghadam-Kia et al., Cleve Clin J Med. 2016; 83(1): 37–42. **24.** Tehrani et al., Electron Physician. 2012;9(7):4886-4889. **25.** www.orpha.net, search: genetic neuromuscular disease, marketing authorization Europe accessed August 2nd 2018. Sanofi Genzyme/GZBE.PD.18.08.0171.