

# Cardiovascular involvement in Pompe disease

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## ABSTRACT

Lysosomal storage diseases are a diverse group of monogenic disorders which are as defined by defects in lysosomal function. The heart is part of the clinical phenotype of lysosomal storage diseases. Pompe disease is marked by absence/deficiency of the lysosomal enzyme alpha-glucosidase and by different ages of onset. The infantile form is defined by muscle weakness and progressive cardiac hypertrophy, followed by progressive cardiac failure. Pompe disease requires immediate intervention to maximize the potential benefit from enzymatic therapy, with improvement of the phenotype. This article presents clinical and cardiac findings suggestive for Pompe's disease.

**Keywords:** lysosomal diseases, Pompe disease, cardiomyopathy

## Lysosomal storage diseases

Lysosomes are single phospholipid bilayer membrane cytoplasmic organelles which contain hydrolytic enzymes. Lysosomal storage diseases (LSD) are a diverse group of monogenic disorders (mostly recessively inherited, few X-linked) which are the consequence of defects in lysosomal function, defined by the accumulation of undigested/partially digested macromolecules, which produce cellular dysfunction and secondary, a multi-systemic pathology (1).

LSD have a frequency of about 1/8000 live births (2).

LSD are mostly produced by the lack of lysosomal hydrolase but defects in post-translational modification proteins, activator proteins or lysosomal trafficking proteins have been reported recently (3).

Recently LSD have been classified according to the molecular defect detected to the patient (defects in glycan degradation, in lipid degradation, in protein degradation, in lysosomal transporters, in lysosomal trafficking) (4,5).

From the clinical point of view the combination of dysmorphic features (coarse facies, macroglossia), bone anomalies (dysostosis), heart anomalies (arrhythmia, cardiomegaly), hepatosplenomegaly

and neurological symptoms (developmental delay, hypotonia, epilepsy, peripheral neuropathy, mental retardation, ataxia/spasticity) may strongly suggest the clinical suspicion of LSD. Classically the symptoms are progressive (6).

The enzymatic test is possible for most LSD. Molecular genetic testing can confirm the enzymatic diagnosis and can clarify the type of genetic variation which is an important information in evaluating enzyme replacement therapy (4).

Genetic counselling for at-risk couples includes prenatal testing on chorionic villi or amniocytes. LSD are inherited as autosomal recessive diseases, except for Fabry disease, Hunter syndrome and Danon disease which are X-linked disorders (4).

## Pompe disease

Pompe disease (glycogen storage disease II) is an autosomal recessive disease, with multisystemic and progressive neuromuscular hypotonia, caused by a mutation in the acid alpha-1,4-glucosidase gene (chromosome 17q25.3) (7).

The estimated **incidence** of Pompe disease (PD) is 1/40,000 (8). The adult form of PD has an incidence of 1/57,000 newborn per year (9).

The incidence of carrier is 1/138,000 for classic infantile disease and 1/57,000 for late-onset disease (10).

The infantile onset PD appears to be more common in African-Americans, in China and Taiwan (11) while the adult form is more frequent in the Netherlands (8).

**In classic form of PD with infantile onset** the patient has severe hypotonia (20-63% cases), cardiac anomalies with congestive heart failure (50-92% cases), macroglossia, feeding difficulties (44-97% cases) and respiratory problems (27-78% cases) (12-14).

**The non-classic variant of infantile-onset PD** is manifested in the first year of life as motor delays and progressive muscular hypotonia. Usually the cardiac involvement is mild. (14,15).

**Late-onset of PD** could be considered in patients with proximal muscular weakness and respiratory insufficiency, with no apparent cardiac involvement (15).

This form manifests after 27-41 years but the early disease manifestations prevail the diagnosis with 3-10 years because the slow and relatively unspecific progression of symptoms (16,17).

Clinical findings should always be confirmed by additional tests. **Nonspecific tests** include serum creatine kinase (which is elevated in classic form of PD and normal in adult onset PD) (18) and urinary glucose tetrasaccharide which is highly sensitive for PD but nonspecific (19).

**The specific tests** are acid alpha-glucosidase (GAA) enzyme activity in blood dried samples which has a low activity. The test is performed before to initiation of therapy. GAA enzyme activity in cultured skin fibroblasts or muscle is the standard test but difficult to perform. (20; 18) The molecular test may help confirm a PD diagnosis and this test is especially used in families where there was already a PD case and is trying to identify carriers of the mutated gene in order to provide genetic counseling (18).

Enzyme replacement therapy with recombinant human acid  $\alpha$ -glucosidase showed an extension of survival and an improvement in cardiac function (21). Some studies revealed that  $\beta$ -Blockers, such as propranolol, may reduce the efficiency of enzymatic treatment by modulating the receptor expression (22).

From the point of view of cardiologists, PD is an important cause of familial hypertrophic cardiomyopathy (23). Cardiac structure and function should be evaluated through echocardiography, EKG and Holter monitoring (24).

**The classic infantile form** of PD is characterised by the presence of **hypertrophic cardiomyopathy** (septal or concentric) in 88% cases, cardiomegaly in 92-100% cases, left ventricular hypertrophy 83-100% cases with or without left ventricular outflow tract obstruction and EKG anomalies (13,14). The cardiomyopathy is related to intracellular glycogen accumulation leading to cellular hypertrophy and decreased systolic function (25).

Levine J.C. et al., in 2008, reported regression of left ventricular hypertrophy and improves the ejection fraction after enzyme replacement therapy with alglucosidase alfa (25).

Glycogen storage involves also the cardiac conduction system (A-V node and the His-bundle cells). The most common **EKG anomalies** are pre-excitation syndromes (short PR in 10% cases, delta waves) on 24 hours ECG Holter (26), Wolff-Parkinson-White syndrome (27,28), atrio-ventricular blocks and bundle branch block in 4% cases (26,29).

The pathogenic mechanism involved in Wolf Parkinson White syndrome is not fully understood. Several hypotheses have been put forward to explain the anomaly: the conduction system is directly affected by the intracellular accumulation of glycogen or anulus fibrosus is anatomically interrupted by accumulation of glycogen. (28,17) Some authors reported elevated plasma BNP (B-type natriuretic peptide) which seems to be related to the severity of cardiac disease (30).

**The non classical form of PD** with infantile onset has less severe clinical manifestations which becomes evident after 1 year age.

Echocardiography reveals a stationary hypertrophic cardiomyopathy, less severe than in classic form of PD and the missing of obstruction or ventricular diastolic dysfunction (31).

**Late-onset PD** it can occur at any age by progressive muscular hypotonia and respiratory insufficiency. Some patients could have arteriopathy with aneurysm of the basilar and internal carotid arteries or dilation of the ascending aorta because the accumulation of glycogen in vascular muscle (32-34). The patients could be asymptomatic or have unspecific neurologic symptoms (transient ischemic attacks and oculomotor nerve paralysis) (33).

Some studies which have been published quite recently reported for adult a short PR interval in 10% cases and a decreased left ventricular systolic function in 7% cases (26). Anaesthesia for patients

with PD could precipitate arrhythmias, cause vasodilation and reduce myocardial contractility (35).

Hypothyroidism and subclinical hypothyroidism have a higher prevalence in patients with late-onset PD as compared to the general population, which could complicate pre-existing cardiac disease (36).

**In conclusion**, routine cardiac evaluation in PD by echocardiography is an essential part of the PD

management, can follow the disease progression and response to intervention. The echocardiography should be performed by a pediatric cardiologist experienced in PD. A 24 hour ambulatory ECG should be performed as a diagnosis baseline of PD to highlight possible arrhythmias.

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