Infantile-onset Pompe disease: Diagnosis and management

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ABSTRACT

Pompe disease, also known as acid maltase deficiency or glycogenosis type II, is a rare severe, autosomal, recessive, and progressive genetic disorder caused by deficiency in alpha-glucosidase.

The classic infantile-onset is the most broadly known form of Pompe disease, which presents with severe heart involvement and clear hypotonia, while the non-classic presentation occurs with early motor involvement. Late-onset Pompe disease develops in adults, but it may also occur during childhood or adolescence.

Here we update the available clinical and diagnostic findings because an early management with enzyme replacement therapy may improve patients' survival and quality of life. We also review the benefits and adverse effects of available treatments and new lines of therapeutic research.

Key words: *Pompe disease, glycogenosis type II, cardiomyopathies, muscular hypotonia, motor disorders.*

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INTRODUCTION

Pompe disease (PD), known as acid maltase deficiency or glycogenosis type II, is a rare severe, autosomal, recessive, and progressive genetic disorder caused by deficiency in acid alpha-glucosidase (*AAG*).[1]

This condition is recognized as the first lysosomal storage disease that was described for the first time by Dutch pathologist Johannes Pompe in 1932, in a female child who died after presenting severe muscle weakness and hypertrophic cardiomyopathy, glycogen storage in the heart, liver, kidneys, and skeletal muscle.[2] In 1979, Hers[3] demonstrated that glycogen accumulation was caused by lysosomal acid maltase deficiency.

The gene related to this enzyme (*GAA*) was identified in the long arm of chromosome 17, and more than 450 mutations have been described.[4]

PD encompasses a broad spectrum of phenotypes, symptoms, age at onset, course, and different organ involvement. There are different presentations: infantile-onset PD (IOPD), late-onset PD (LOPD), and intermediate forms.

The combined incidence of all clinical forms of PD has been estimated to range between 1:40 000 and 1:300 000, depending on studied ethnic origins and geographic areas.[5]

CLINICAL DESCRIPTION AND NATURAL COURSE

The adopted denomination was that proposed by the American College of Medical Genetics (ACMG),[6] including the most commonly described form: classic infantile-onset PD (CIOPD), which occurs with severe cardiomegaly, hepatomegaly, hypotonia since birth, and early death; the non-classic infantile-onset form (NCIOPD), which occurs as of one year old but with a slower progression and less severe cardiomyopathy;[7,8] and late-onset PD (LOPD), which occurs during childhood or adolescence and in adults, between the second and sixth decade of life with slowly progressive myopathy, in general, without cardiomyopathy.

CIOPD occurs at a median of 2 months old (0-12) with feeding difficulties and failure to thrive in 44-97 % of cases, cardiomyopathy in 50-92 %, hypotonia in 20-63 %, and respiratory distress in 27-78 %.

The mean age at the time of death was reported to be 8.7 months (0.3-73); survival at 12 months of age was

25.7 % and, in the group that survived without assisted ventilation, it was 16.9 %. At 18 months of age, survival was 12.3 % and 6.7 %, respectively.[7,9]

The early symptoms of NCIOPD include delay in motor maturation and muscle weakness, with a median age of 2.6 years (0.5-13) at onset and of 4 years (0-16) at diagnosis.[10]

Neuromuscular manifestations

These occur in CIOPD between 0 and 4 months old and include hypotonia since birth, hyporeflexia or areflexia, and muscle weakness in the face (distinctive facies), trunk, and limbs. The proximal muscles of the lower limbs are the most affected ones. Compensatory movement patterns appear due to the extensive weakness and little mobility, thus causing joint deformities and retractions. Orolingual and diaphragmatic muscle weakness has an early effect on swallowing and respiratory function, producing delays in expressive language.[9-11]

In NCIOPD, the neck flexor muscles are the most affected ones, thus hindering the possibility of lifting the head while lying down. Proximal muscle weakness in the limbs leads to frequent falls and difficulty climbing stairs, running, and doing sports. Myopathic facies, scoliosis, and areflexia are described in 50 % of children. Neither dysphagia nor language disorders were observed, except in one case.[12]

In LOPD (children, adolescents, adults), patients have progressive muscle dysfunction in the proximal muscles of the lower limbs and paratruncal muscles, followed by the diaphragm and accessory respiratory muscles.[13]

Respiratory manifestations

In CIOPD, respiratory insufficiency results in early morbidity and mortality. Respiratory muscle weakness and the alteration in cough and swallowing mechanism cause upper respiratory tract infection and repeated pneumonia.[14]

In NCIOPD, 48 % of children have a reduced forced vital capacity and, at a median age of 9 years (range: 5-16 years), they require assisted ventilation or die.[6]

Sleep-disordered breathing presents with lethargy, irritability, nocturnal snoring or sleep apnea.[15]

Heart manifestations

In CIOPD, ventricular hypertrophy, which is predominant on the posterior wall of the left ventricle and the interventricular septum, may appear even while in the uterus. Left ventricular outflow tract obstruction may occur. A rapid and progressive course results in dilated cardiomyopathy with end-stage heart failure. The ejection fraction decreases as of 5 months old. Glycogen storage may lead to conduction disorders, severe ventricular arrhythmias, inadequate coronary perfusion, subendocardial ischemia, and risk for sudden death.[16]

Heart involvement was observed in only 10 % of NCIOPD cases.[11]

Gastrointestinal and nutritional manifestations

In infants, facial hypotonia, macroglossia, and oral motor weakness cause difficulty sucking, thus affecting growth and weight gain. Muscle weakness may lead to dysphagia, gastroesophageal reflux, gastroparesis, and constipation. Hepatomegaly and/or splenomegaly may also occur.[14]

Ancillary tests and diagnostic methods *(Table 1)*

Muscle damage causes an increase in creatine phosphokinase (CPK) (1500 IU or 2000 IU) and liver transaminases.[17]

- **Electrocardiogram:** It helps to show cardiomyopathy with ventricular hypertrophy and heart rhythm disorders; short P-R interval, and very wide QRS complex.[6,18]
- **Electromyography:** In IOPD, an electromyography shows membrane irritability and denervation activity, with high-frequency repetitive discharges. Myotonic discharges may occur in the absence of clinical myotonia. Voluntary contraction shows short, low amplitude polyphasic motor unit action potentials.[19] In LOPD, findings are compatible with proximal muscle myopathy and/or denervation activity in paravertebral muscles.[20]
- **Imaging tests:** A chest X-ray in CIOPD shows cardiomegaly, lung volume reduction and/or areas of atelectasis. In LOPD, it is usually normal.[7]

  A magnetic resonance imaging (MRI) is very useful in LOPD; it helps to establish the pattern and extent of muscle involvement.[21]
- **Enzyme activity:** It is critical for diagnosis; it is measured using a fluorometric assay, a colorimetric assay or a tandem mass spectrometry. Given its accessibility and timeliness, the first diagnostic test is that done on blood spots dried on filter paper. A positive result must be confirmed in lymphocytes, leukocytes, muscle or fibroblasts; the latter

is the *gold standard* diagnostic test, but it is an invasive procedure and results may take up to 6 weeks.[22]

According to the mass spectrometry, blood and fibroblast measurements are comparable.[23-25]

Biochemical tests in addition to enzyme activity

Glucose tetrasaccharide (Glc4) level is an ancillary urinary biomarker of enzyme activity used to assess treatment response. Clearly high Glc4 levels have been reported in IOPD, unlike in LOPD.[26]

Muscle biopsy

A specimen from the most clinically affected area will help to determine the diagnostic hypothesis of PD or guide towards an alternative diagnosis.[27,28]

CIOPD presents with severe vacuolar myopathy and glycogen storage, positive periodic acid Schiff (PAS) staining, and positive acid phosphatase (lysosomal and autophagy marker). Myofibrils are reduced, which may be observed by myosin ATPase. At an ultrastructural level, it is common to see intra- and extra-lysosomal glycogen, structure distortion with a marked reduction in myofibrils and autophagic vacuoles.

In LOPD, biopsies may be normal or show severe characteristics similar to those of IOPD.

A biopsy suggestive of PD must be confirmed with a deoxyribonucleic acid (DNA) or enzymatic diagnostic test.[29]A normal or non-specific biopsy does not exclude PD diagnosis.

Molecular tests (DNA)

The *GAA* gene in chromosome 17q25 has 20 exons. It produces a 952-amino acid protein. Among the more than 500 sequence feature variants, more than 350 display a certain level of pathogenicity, approximately 90 were classified as non-pathogenic mutations and more than 90 had an uncertain significance.[30] Alterations include nonsense, missense, *splicing*, deletion, insertion, and other types of mutations.[4]

Almost 50 % of Caucasian patients with LOPD have the intronic mutation c.-32-13T>G, which affects *splicing* and has never been observed in IOPD, so its presence in one of the alleles would exclude it.

There is no strict genotype-phenotype correlation, but the presence of nonsense mutations in both gene alleles –which result in a truncated protein– is associated with CIOPD.

Other factors (genetic and environmental) may affect the phenotype, so patients with the same mutations may have clinically different phenotypes. Genetic analysis, if the index case is known, helps to establish an antenatal diagnosis and identify carriers.[31]

There is pseudo AAG deficiency, with a reduced *in vitro* enzyme activity; however, *in vivo* activity is enough to prevent PD development. Diagnosis is based on the presence of c.1726G>A (p.G576S) and c.2065G>A (p.E689K) mutations in the same allele (in *cis*) and in homozygosity.

It is advisable to study the family members of patients with a confirmed diagnosis who are at

TABLE 1. *Ancillary tests and diagnostic methods*

Ancillary tests	Findings
CPK	Increase to not more than 1500-2000 IU/L.[25,5]
GOT, GPT, LDH	Increase.[26]
Chest X-ray	Cardiomegaly.[7]
Electrocardiogram	Short P-R interval, wide QRS complex.
Echocardiogram	Hypertrophic cardiomyopathy with or without outflow tract obstruction. In late stages, dilated cardiomyopathy.[5,8]
Electromyography	Infantile-onset form, high-frequency repetitive discharges, myotonic discharges, short, low amplitude polyphasic MUAPs with voluntary contraction. Late-onset form, proximal muscle myopathy without denervation activity or restricted to specific groups, such as paravertebral muscles.[27-29]
MRI (not routinely indicated)	Greater involvement of axial muscles; universal involvement of lumbar paravertebral muscles and psoas. T1 images are enough for an adequate assessment.[30]
Peripheral blood smear (to be assessed)	Vacuolated PAS-positive lymphocytes.

CPK: creatine phosphokinase; PAS: periodic acid Schiff staining; MUAP: motor unit action potential; MRI: magnetic resonance imaging; GOT: glutamic oxalacetic transaminase; GPT: glutamic pyruvic transaminase; LDH: lactate dehydrogenase.

risk, especially their siblings due to the recessive nature and the possibility of PD remaining silent for a long time.[32]

Differential diagnoses *(Tables 2 and 3)*

In CIOPD, the main signs are cardiomegaly and hypotonia. It is necessary to distinguish between cardiomegaly and viral myocarditis, hypertrophic cardiomyopathy, mitochondrial diseases, carnitine transport defects, and fatty acid oxidation.

Severe hypotonia in an infant must be distinguished from infantile-onset spinal muscular atrophy, muscular dystrophies, and congenital myopathies. LOPD must be distinguished from other neuromuscular disorders. Supplementary tests will help with diagnosis.

MANAGEMENT

General measures

Although a specific treatment has been established since 2006, general and palliative measures are still critical:

- Complete immunization schedule, including pneumococcal and influenza vaccines and respiratory syncytial virus prophylaxis. Intensive and early management of respiratory conditions. Suction and phonation should be encouraged. Oral or nasogastric or gastrostomy tube feeding should be maintained, as per the patient's needs.[33]
- Hearing equipment should be used in the presence of sensorineural hearing loss, which may occur in IOPD.[34] Follow-up with an experienced cardiologist is necessary because commonly used drugs may be contraindicated in certain stages of PD.[6]

TABLE 2. *Differential diagnoses in the "classic infantile-onset" form*

Common signs and symptoms	Relevant conditions
Hypotonia, progressive proximal muscle weakness, areflexia, respiratory insufficiency	Infantile-onset spinal muscular atrophy type 1 Congenital neuropathy Congenital myopathy (+/- MR)
Hypotonia, macroglossia	Hypothyroidism, trisomy 21
Hypotonia, hepatomegaly	Peroxisomal disorders
Hypotonia, muscle weakness, and high CPK	Muscular dystrophies Beta-oxidation disorders Mitochondrial diseases
Biventricular hypertrophy	Idiopathic hypertrophic cardiomyopathy
Hepatomegaly, cardiomegaly, cardiomyopathy, respiratory involvement, muscle weakness, hearing impairment	Mitochondrial disease, respiratory chain
Cardiomegaly, dyspnea, respiratory insufficiency, feeding difficulties	Congenital heart anomalies Myocarditis
Cardiomyopathy, myopathy, high CPK, hypotonia Cardiomegaly, hypertrophic cardiomyopathy, myopathy, hypotonia	Glycogen storage disease type III.a and IV
Vacuolar glycogen storage	Danon disease

MR: myotatic reflexes; CPK: creatine phosphokinase.

TABLE 3. *Differential diagnoses in the "non-classical infantile-onset" form as of one year old*

Common signs and symptoms	Relevant conditions
High CPK, proximal weakness	Limb-girdle muscular dystrophy
Muscle weakness, respiratory distress	Duchenne and Becker muscular dystrophy
High CPK, exercise intolerance	Glycogen storage disease type V (McArdle disease)
Hypotonia, muscle weakness, high CPK	Glycogen storage disease type VI
Proximal and neck muscle weakness, high CPK	Inflammatory myopathies (polymyositis, dermatomyositis)
Muscle weakness, respiratory involvement, arrhythmias	Mitochondrial disease, respiratory chain
Progressive proximal weakness, respiratory involvement, scoliosis	Motor neuron disease, infantile-onset spinal muscular atrophy type 2-3

CPK: creatine phosphokinase.

- Bending postures should be avoided, vertebral alignment should be maintained, and physical exercise, orthoses or supportive products should be used if necessary.[35,36]

Specific treatment

The specific treatment available for PD at all ages is enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase (rhAAG), alglucosidasealfa (Myozyme®, Genzyme Corporation), approved for the United States by the Food and Drug Administration (FDA) in 2006,[37,38] based on a study that included a control group with 8 patients for 52 weeks, which has been complemented with the multiple treated cases published in the past 12 years.[10,16,31,39,40-43]

Comped to the natural course, CIOPD patients receiving early ERT have an improved life expectancy and heart function and a reduction of cardiomegaly.[44] Improvements in muscle tone and strength depend on treatment timeliness and mutation severity. Patients do not always achieve significant motor independence. Respiratory and swallowing functions and growth stabilize. The quality of life improves but remains affected.[45]

TREATMENT EFFECTIVENESS

Cross-reactive immunologic material status

Before starting ERT, it is necessary to establish whether the patient produces or not cross-reactive immunologic material (CRIM) because this determines treatment effectiveness.

Patients with null mutations, which occur in 25-30 % of CIOPD cases, do not produce AAG at all, so they lack such material (CRIM negative). In these cases, the infused enzyme will be recognized as a foreign protein and produce high neutralizing antibody titers, which will override its effect. In these cases treated with ERT, the initial improvement may be followed by a significant clinical deterioration.[46,47]

Patients with a certain level of their own AAG protein, although inactive, are CRIM positive; in them, infused rhAAG will not be recognized as a foreign protein and antibody titers will remain low and treatment will be more effective.

CRIM status is established before starting ERT in blood samples kept at -80 °C or in fibroblast cell culture. If determination becomes difficult, it is necessary to study mutations to infer CRIM status.[48]

Immune tolerance induction

In CRIM-negative patients, immune tolerance to ERT may be induced, ideally before starting treatment at an experienced facility, with drugs such as rituximab and methotrexate and a monthly gamma globulin support. This will suppress immune response.[49]

Enzyme replacement therapy indication

ERT is indicated to every patient with symptomatic IOPD, clinical and enzymatic diagnosis, CRIM test or genetic test.[38] ERT dose is 20 mg/kg every two weeks as per preparation and infusion indications of the manufacturing company.[29]

There is no wide consensus about the fact that a higher or more frequent dosage improves survival or quality of life, but it could lead to greater adverse events.[50]

ERT is not indicated in the presence of other life-threatening diseases or in very severe cases with invasive ventilation due to non-acute respiratory failure.[38]

It is an expensive treatment and, until national health authorities decide on its use, it is suggested that it should only be indicated in patients with confirmed diagnosis upon consultation with a group of health care providers with experience in PD and its management.

Adverse events of enzyme replacement therapy

As any protein infusion, it may cause allergic reactions due to immunoglobulin G (IgG) antibodies.[51]

In general, these are mild or moderate reactions and are controlled by slowing the infusion rate or temporarily interrupting it until manifestations are resolved; also, antihistamines and corticosteroids may be used as premedication. As an isolated event, a severe anaphylactic reaction may occur due to immunoglobulin E (IgE) antibodies, which reinforces the need for infusion in a hospital setting.

The patient's family should be aware of the expected actual benefit and the risk for complications.

New treatments

Other specific treatments[52,53] are being developed, including gene therapy,[54] autologous hematopoietic cell transplantation in association with lentivirus,[55] chaperone use,[56] second-generation recombinant ERT, and substrate reduction therapy, but their clinical benefits have not been demonstrated yet.[52,54]

New phenotype in patients with classical infantile-onset Pompe disease receiving enzyme replacement therapy

ERT with AAG resulted in a new phenotype.[35] It is not a shift from the classical phenotype to the late-onset phenotype but one with specific clinical characteristics.

The largest study done in this regard[57] described 11 patients aged 5.4-12 years who were CRIM positive, had symptoms before 6 months old, had enzyme activity < 1 %, did not require ventilatory support and started ERT before 6 months old and survived for more than 5 years. At 5 months of ERT initiation, their cardiomyopathy was resolved. Five of the 11 patients had some type of manageable arrhythmia. No patient required ventilatory support; two of them had obstructive sleep apnea syndrome. Seven of the 11 patients achieved independent gait, while the rest required some sort of support. Most patients showed generalized, residual weakness associated with hypotonia, predominant in the neck muscles, the proximal muscles of the lower limbs (hip extensors, adductors and abductors), the tibialis anterior with foot dorsiflexion difficulty, and the muscles of the face with facial hypomimia, while five of the 11 patients had ptosis. Ten had nasal speech; 5, dysphagia; 7 were exclusively fed by mouth; 9, had conductive or sensorineural hearing loss. Growth was normal, except in one patient, and six had osteopenia, which was severe in two cases. CPK levels did not return to normal until 24 months after starting the ERT.

The cognitive level at school age was normal or mildly reduced in 10 patients with CIOPD who survived with ERT. This had been underestimated before 5 years old in relation to motor involvement.[58]

An eye examination allowed to detect myopia, astigmatism, and ptosis in an early manner so as to prevent amblyopia.[44]

It has also been pointed out that, at the level of the central nervous system (CNS), an initial ventricular dilation improves with ERT; however, in some patients, changes may occur in the periventricular white matter, together with abnormal signals at the basal nuclei and brain aneurysms.[40]

Although ERT has improved the survival (grade 3 evidence) and quality of life of most children, the course of PD is variable due to factors such as age at ERT initiation, level of disease involvement, genotype, CRIM status, a muscle biopsy with predominance of fibrils and autophagy, and a high level of autoantibodies during treatment.[41,42]

FOLLOW-UP

Treatment effectiveness should be assessed through a careful, regulated follow-up by a multidisciplinary team coordinated by a health care provider with experience in PD *(Annex: Clinical follow-up record)*. Patient improvement or stabilization give the indication to continue with ERT.[59] ■

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ANNEX.

Clinical follow-up record. Modified from reference[59]

Clinical follow-up record **Control**												
Months old	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**18**	**24**	**> 24**
Weight, height, HC, growth rate	x	x	x	x	x	x	x	x	x	x	x	e/6
Feeding reminder	x	x	x	x	x	x	x	x	x	x	x	months
Laboratory: clinical-nutritional, CPK, GOT, GPT, GGT, tetrasaccharides, antibodies	x			x				x	x	x	x	
Intake observation	consistent with visit											
Video fluoroscopic swallowing exam	as per clinical assessment											
Gastrointestinal series	if gastroesophageal reflux is suspected											
Echocardiogram	x	x	x	x	x	x	x	x	x	x	x	e/6
Electrocardiogram	x	x	x	x	x	x	x	x	x	x	x	months
Holter ECG	x						x		x	x	x	
RR	x	x	x	x	x	x	x	x	x	x	x	
Chest X-ray (due to atelectasis or other concurrent condition) as per clinical assessment	x											
Pulse oximetry in recumbent position and sitting down + capnography	x	x	x	x	x	x	x	x	x	x	x	
Blood gases	x			x			x	x	x	x	x	
Crying VC	x			x			x	x	x	x	x	x
Polysomnography	x			x					x		x	
Sputum test (as needed)												
Neurological/musculoskeletal exam	x	x	x	x	x	x	x	x	x	x	x	x
Neurodevelopment	x			x			x					x
Hearing assessment	x								x			x
Eye examination	x								x			x

HC: head circumference; CPK: creatine phosphokinase; GOT: glutamic oxalacetic transaminase;
GPT: glutamic pyruvic transaminase; GGT: gamma-glutamyltransferase; RR: respiratory rate; VC: vital capacity.