Clinical guidelines for late-onset Pompe disease

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Summary. Before 2006, Pompe disease or glycogenosis storage disease type II was an incurable disease whose treatment was merely palliative. The development of a recombinant human alpha-glucosidase enzymatic replacement therapy has become the first specific treatment for this illness. The aim of this guide is to serve as reference for the management of the late-onset Pompe disease, the type of Pompe disease that develops after one year of age. In the guide a group of Spanish experts make specific recommendations about diagnosis, follow-up and treatment of this illness. With regard to diagnosis, the dried blood spots method is essential as the first step for the diagnosis of Pompe disease. The confirmation of the diagnosis of Pompe disease must be made by means of an study of enzymatic activity in isolated lymphocytes or a mutation analysis of the alpha-glucosidase gene. With regard to treatment with enzymatic replacement therapy, the experts say that is effective improving or stabilizating the motor function and the respiratory function and it must be introduced when the first symptoms attributable to Pompe disease appear.

Key words. Alpha-glucosidase. Dried blood spots. Enzymatic replacement therapy. Late-onset. Mutation analysis. Pompe disease.

Introduction

Glycogen storage disease type II or Pompe disease (OMIM Entry # 232300), also referred to as acid maltase deficiency, is a rare lysosomal storage disease characterized by the accumulation of glycogen primarily in muscle tissue. It is an autosomal recessive inherited disease in which there is a deficiency in the activity of the lysosomal enzyme acid α-glucosidase. The α-glucosidase gene is located on the long arm of chromosome 17 (17q25.2-q25.3) [1]; more than 350 mutations have been identified, which are catalogued at the Pompe Center of the Erasmus MC in Rotterdam [2]. The most common mutation in Caucasian patients is IVS 1 (–13T>G), present in one of the alleles of more than 50% of individuals with Pompe disease.

Before 2006 it was an incurable disease for which there was only palliative treatment. The development of replacement therapy using the recombinant human acid α-glucosidase enzyme constituted the first specific treatment for Pompe disease [3].

The steady accumulation of glycogen in tissues can lead to increased weakness, organ failure and ultimately death. The severity varies according to the age of onset, rate of progression of organ involvement and muscle involvement [4]. In fact, variability is so great that, although most of those affected have trouble getting up or climbing stairs, there are others who are virtually asymptomatic [5].

Infantile- and late-onset Pompe disease are the two most common forms of the disorder. The infantile form is the most severe type and is characterized by cardiomegaly, generalized muscle weakness, hypotonia, hepatomegaly and death from respiratory failure before the end of the first year of life. Although the clinical presentation of classic infantile-onset Pompe disease is quite homogeneous and corresponds to the one described by Pompe in 1932 [6], there is also a less severe non-classic form described by Hers [7]. The late-onset form, also known as juvenile or adult form, appears after the age of one and affects skeletal muscle, causing progressive muscle weakness and respiratory impairment. In the late-onset form, respiratory complications often have severe clinical repercussions. The different forms are generally correlated with α-glucosidase activity, which in affected infants under the age of 1 is usually less than 1% of normal activity, while in the juvenile form it is less than 10% and in adults less than 40%.

The incidence of early-onset Pompe disease among the Taiwanese and Dutch populations is 1 in 33,333 and 1 in 138,000 respectively. The incidence of late-onset Pompe disease is estimated to be 1 in 57,000. Newborn screening programs for Pompe disease

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With the scientific backing of:
Spanish Society of Internal Medicine (SEMI), Spanish Society of Neurology (SEN) and Spanish Society of Pneumology and Thoracic Surgery (SEPAR).

Conflict of interest statement:
The authors thank Genzyme S.L.U. →

Table I. Differential diagnosis of late-onset Pompe disease.

Diseases for which it can be mistaken	Findings in common
Duchenne, Becker and limb-girdle types of muscular dystrophy	Progressive muscle weakness in shoulders, pelvis and lower limbs, elevation of CK
Scapulohumeral syndromes	Weakness of shoulder girdle, winging of scapula
Myotonic dystrophy-2	Proximal muscle weakness, fatigue, cramps, irritative electromyogram, elevation of CK
Rigid spine syndrome	Limited mobility of the spine, low back pain, axial muscle weakness
Myasthenia gravis	Fatigue and generalized muscle weakness, respiratory distress
Spinal muscular atrophy	Muscle weakness and atrophy, elevation of CK
Polymyositis	Subacute proximal muscle weakness, elevation of CK
Glycogen storage disease types IIIa, IV, V and VII	Hypotonia and hepatomegaly in childhood, muscle weakness, exercise intolerance, elevation of CK
Danon disease	Hypertrophic cardiomyopathy, vacuolar myopathy with glycogen storage, elevation of CK
Mitochondrial myopathies	Muscle weakness, exercise intolerance, cardiomyopathy and elevation of CK
Asymptomatic hyperCKemia	Elevation of CK

CK: creatine kinase.

for the support given to the committee for the production of this guide and Content Ed Net for its assistance with drafting it. Genzyme S.L.U. revised the manuscript to ensure the accuracy of all statements about company-sponsored clinical trials, but was not involved in the literature review, formulation of recommendations or the production and revision of the guidelines.

Accepted: 15.02.12.

How to cite this article: Barba-Romero MA, Barrot E, Bautista-Lorite J, Gutiérrez-Rivas E, Illa I, Jiménez LM, et al. Clinical guidelines for late-onset Pompe disease. Rev Neurol 2012; 54: 497-507.

Versión española disponible en www.neurologia.com

have recently been started in Taiwan, Austria and some areas of the United States [8].

Methods

The purpose of this guide is to serve as a reference for the management of late-onset Pompe disease. Specific recommendations are made regarding the diagnosis, monitoring and treatment of this disease.

The working group that has developed this guide includes specialists in all of the professional disciplines involved in caring for patients with Pompe disease: neurology, pulmonology, pediatric neurology, internal medicine, biochemistry and genetics. Patient perspectives and preferences have been taken into account; the users of the guide are clearly defined.

To produce this guide a literature search of the TRIP, Cochrane Library, Cochrane Plus, EMBASE, PubMed/Medline and ECA LOST databases was performed using the PICO (patient, intervention, comparison, outcome) method recommended by the National Health System's CPG working group [9]. The search terms used were 'Pompe disease' and 'late-onset' acid α-glucosidase deficiency, maltase deficiency, glycogen storage disease type II and glycogenosis type II. No date was specified. The references in the articles found were also used. The most recent papers and those that met the highest standards of scientific quality were selected as sources of evidence. The Scottish Intercollegiate Guidelines Network (SIGN) criteria were used to establish the levels of evidence and determine the grades of recommendations for this guide [10].

The articles reviewed were used by the authors to prepare a scoping document that was revised on several occasions by all of them. The conclusions reached were agreed upon at a working session held in Madrid on October 4, 2011. Later, two teleconferences were held to shape the guide into its final form.

The difficulties involved in implementing the approved recommendations were discussed during the preparation of the guide, as were the potential costs.

The authors represent the national committee of experts on Pompe disease, a panel of doctors with extensive clinical experience of the disorder. Responsibility for the interpretation of this review rests with the authors. All authors have approved the final version of the manuscript and are fully responsible for its content.

Diagnosis

Early diagnosis is vital in symptomatic Pompe disease. It is one of the few myopathies whose natural course may be altered, which is why a delay in diagnosis may be harmful for the patients. It is of utmost importance that physicians in general and primary care physicians in particular should consider the possibility of this disease in patients who present with muscle fatigue, clumsiness, difficulty in breathing and/or elevated muscle enzymes.

The late-onset form is clinically very heterogeneous, which makes it difficult to diagnose it because it can mimic other neuromuscular disorders (Table I) [5].

Signs and symptoms of late-onset Pompe disease

Clinical presentation of late-onset Pompe disease may vary considerably with respect to the age of onset, organ involvement, degree of myopathy, and rate of progression (Table II). The disease is usually

progressive and its course does not always correlate with the age of onset [11].

Late-onset Pompe disease may occur at any time after the age of one and usually presents with a progressive myopathy [12]. Weakness is preceded by myalgia and muscle cramps. Children have a developmental delay in motor skills [13]. Adults experience proximal muscle weakness, which is greater in the muscles of the pelvic girdle, making it difficult to climb stairs, run or get up from a chair.

Respiratory failure is the leading cause of morbidity and mortality [14] so attention must be paid to the development of symptoms of respiratory distress, especially when in a supine position, caused mainly by diaphragmatic involvement, and infections, which shall require early and aggressive therapeutic intervention. The progression of muscular weakness and respiratory symptoms causes some patients to require wheelchairs and mechanical ventilation. In the study by van der Beek et al [15] in which 16 patients were followed for an average of 16 years, patients presented with a 1.6% annual decline in lung function, 50% ended up needing a wheelchair and 19% required mechanical ventilation. In patients with late-onset Pompe disease, respiratory failure may be mild and go unnoticed [16,17].

Other serious complications are those resulting from the presence of intracranial aneurysms, which may be underdiagnosed and cause death due to the disease [18].

Since the early symptoms of late-onset Pompe disease are non-specific, it often takes several years to reach the correct diagnosis. Thus, the review by Hagemans et al showed that diagnostic delay ranged from 5 to 30 years in a third of the cases [12].

The weakness affects the pelvic girdle rather than the scapulohumeral muscles and affects the proximal muscles more than the distal muscles [12]. Muscular atrophy tends to be proportionate to the degree of paresis, but there are patients with no detectable weakness. In fact, nearly half of patients with late-onset Pompe disease have pain in one or more areas of the body and it was found that 76% complain of fatigue [5].

Other problems that can be found in the first evaluation are difficulties with chewing or jaw muscle fatigue, a weak gag reflex and difficulty in swallowing [4].

Table II. Signs and symptoms during an initial assessment of late-onset Pompe disease.

Musculoskeletal system
Progressive limb-girdle weakness (pelvic muscles are affected more than the scapulohumeral group)
Amyotrophy
Hyporeflexia
Gait disturbances
Exercise intolerance (early tiredness and fatigue)
Myalgia and cramps
Contractures and deformities such as lordosis and scoliosis (children)
Delay of motor development (children)
Respiratory system
Dyspnea on exertion
Orthopnea
Respiratory problems while sleeping, sleep apnea/hypopnea syndrome with daytime sleepiness and morning headache
Weak cough
Frequent respiratory infections
Others
Subarachnoid hemorrhage due to ruptured brain aneurysm (especially in the basilar artery)
Dysphagia
Difficulty chewing
Weight loss

Tests and clinical studies to reach a diagnosis

Several tests should be performed in patients suspected of having Pompe disease to lead us to the diagnosis (Table III).

Clinical evaluation must include manual assessment –Medical Research Council (MRC) scale– or quantification of muscle strength together with the performance of basic functional tests such as the Gowers maneuver and gait assessment. The use of quantitative scales or standardized timed tests is always desirable although dependent on the availability at each institution and there may be restrictions on their use, as they consume time and resources. However, they are essential in the evaluation of late-onset Pompe disease.

Elevations of CK, transaminase (ALT, AST) and LDH levels are sensitive but non-specific indicators for late-onset Pompe disease as they can be seen in 95% of those affected [19]. Transaminase elevation in the presymptomatic stages can lead to a mistaken

Table III. Diagnostic protocol when late-onset Pompe disease is suspected.

Clinical evaluation including manual or quantitative assessment of muscle strength (Medical Research Council scale) and basic functional tests (e.g. Gowers maneuver)
Blood biochemistry analysis (CK, ALT, AST, LDH)
Spirometry and change in forced vital capacity in sitting and lying supine positions (for children who cannot follow instructions, respiratory infections should be recorded)
Dried blood spot test
Enzyme analysis of α-glucosidase in lymphocytes and other tissue samples (enzymatic confirmation of diagnosis)
Genetic study
Other tests that will help make a diagnosis: Urine analysis (glucose tetrasaccharide-Glc4) Muscle biopsy Electromyogram Muscle imaging (MRI) Polysomnography and nocturnal oximetry Electrocardiogram, echocardiogram and chest X-ray
Diagnostic confirmation: Genetic testing: analysis of mutations in the acid α-glucosidase gene Enzyme studies: acid α-glucosidase activity in lymphocytes

diagnosis of liver disease, especially if CK has not been measured.

Although it may also be found in other glycogen storage diseases, elevation of urinary glucose tetrasaccharide (Glc_4) supports the diagnosis of Pompe disease if compatible with clinical findings [20].

Spirometry is very useful for detecting the signs of respiratory impairment that are common in late-onset Pompe disease, and may even occur in the presymptomatic stage. Measurement of forced vital capacity (FVC) should be made in the sitting and lying supine positions. A decrease by more than 10% in FVC from sitting to lying supine position suggests weakness of the diaphragm [17].

Electrophysiological tests in patients with Pompe disease usually reveal normal nerve conduction, but the electromyogram (EMG) may show a myopathic pattern of the proximal muscles and signs of membrane irritability with myotonic discharges, usually in the paravertebral muscles [21].

Muscle imaging techniques may also be useful, especially magnetic resonance imaging (MRI). Generally speaking, it has been shown in myopathies that muscle weakness correlates with abnormal MRI findings. No specific distribution of muscle atrophy and fatty infiltration has been observed in patients with Pompe disease [22], but use of a whole body MRI protocol can show a pattern suggestive of this disease [23]. It is also possible to use quantitative methods that may be useful in following the course of the disease and in the assessment of treatment outcomes [24].

Muscle biopsies from these patients show vacuolar myopathy with glycogen storage, although they may be normal or nonspecific in 30% of cases [25].

Measurement of α-glucosidase activity in dried blood spots is essential for the diagnosis of late-onset Pompe disease. The finding must be confirmed by an enzyme assay performed in isolated lymphocytes in a liquid sample [3].

Given its high specificity and sensitivity, mutation analysis of the α-glucosidase gene may be performed as a confirmatory test; over 350 mutations have been described up to the present time.

Diagnostic confirmation

In light of the findings set out in table IV, the likelihood of late-onset Pompe disease is high and it would only be necessary to obtain a confirmation of the diagnosis (Figure).

There are two ways to confirm a diagnosis of late-onset Pompe disease, through a second assay to confirm reduced activity of the acid α-glucosidase enzyme or through molecular genetic analysis (Table III).

In children and adults with late-onset Pompe disease, a genetic study including a complete molecular analysis of the acid α-glucosidase gene is highly recommended, as it is useful for confirming the diagnoses especially when enzyme activity values are not entirely conclusive because they are within the limits of normal range. For information about all laboratories offering full gene sequencing of the α-glucosidase gene, see genetests.org [26]. In some cases this may be valuable in predicting patient outcome [28].

Management

In order to provide appropriate care and treatment to patients diagnosed with late-onset Pompe disease, both multidisciplinary and transdisciplinary approaches are necessary to allow the specialists to jointly collaborate and coordinate. The team of professionals must include a physician with experience

in managing Pompe disease, who will coordinate the team. Team members should include specialists in the fields of neurology, pulmonology, general medicine (internal medicine, pediatrics, metabolism), occupational therapists and disease geneticists.

General medical care recommendations

The health of patients who have late-onset Pompe disease becomes progressively more fragile, so special care must be provided and attention paid to situations that in other cases would be trivial.

- Strict hygiene measures must be followed.
- Nutritional status must be assessed and a diet followed where 25-30% of calories come from protein recommended.
- Treatment of infections, especially respiratory infections, should be aggressive and should include use of antivirals for the flu.
- Routine vaccinations should be administered, following local guidelines for populations at risk.
- Care should be taken with drugs that have a myorelaxant effect and central nervous system depressants.
- With respect to general anesthesia there are no absolute contraindications. Monitoring respiratory function is recommended.
- The family should be educated about the disease and the recommendations for improving outcome.
- Encourage social interaction at regular intervals.

Pulmonary involvement

As Pompe disease progresses, the respiratory muscles become weaker until respiratory function values are altered, the cough becomes weak, there are alterations in gas exchange and respiratory disturbances appear during sleep [28].

When lungs are affected:

- Respiratory function should be monitored periodically for signs of respiratory muscle weakness and/or sleep disorders.
- Spirometry and measurement of oxygen saturation by pulse oximetry should be done at every check-up.
- An arterial blood gas (ABG) test should be performed annually or when there are any changes in the respiratory status.
- Initial chest X-ray and whenever there are changes in the respiratory status.
- Respiratory physiotherapy and manual and/or mechanical-assisted coughing techniques should be started early.

Table IV. Findings suggesting the presence of Pompe disease (modified at [8]).

Test	Findings
Manual assessment of muscle strength (MRC scale) and functional tests	Weakness predominantly affecting proximal muscles
	Gowers' sign, difficulty climbing stairs
Creatine kinase	May be normal or up to 15 times above the normal limit
Spirometry	≥ 10% reduction in forced vital capacity when moving from sitting to lying supine position
Electrophysiological studies	Nerve conduction study: normal
	Electromyogram: signs of irritability of the muscle membrane (sometimes only in the paravertebral muscles). Motor unit potentials are of low amplitude, short duration and polyphasic
Polysomnography	Desaturation indexes (apnea-hypopnea index, etc.)
α-glucosidase activity in DBS or peripheral blood lymphocytes	Variable reduction of α-glucosidase activity, which can reach < 10% to < 40% of normal activity

DBS: dried blood spots; MRC: Medical Research Council.

- Assessment of respiratory function during sleep needs to be made whenever there is hypoxemia and/or daytime sleepiness, morning headaches or sleep apnea has been observed.
- Oxygen therapy and/or positive pressure ventilation should be prescribed according to the problems detected: hypoxemia, obstructive sleep apnea, hypoventilation.
- Sedatives should be avoided and respiratory infections should be treated immediately.

Digestive system disorders and nutritional problems

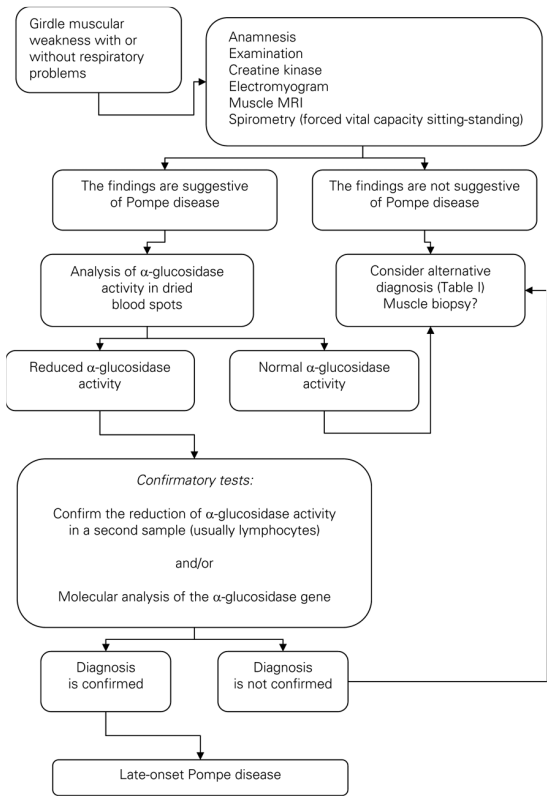
The first complaints of patients with late-onset Pompe disease may be related to jaw muscle fatigue and difficulties with chewing and swallowing. This may lead to an inadequate intake of calories, vitamins and minerals that can cause protein deficiency, which will further aggravate problems with the muscles.

Nutrition is very important for maintaining optimal lysosomal function.

When there are gastrointestinal and nutritional problems:

- Videofluoroscopic evaluation of oropharyngeal swallowing.
- Monitor growth parameters in young patients.
- Recommend a diet with a protein intake of about 25-30% of total calories.

Figure. A diagnostic algorithm for late-onset Pompe disease.



– Reduce carbohydrate intake.
– Vitamin and mineral supplements.
– Use thickeners to make swallowing liquids more manageable.
– Recommend exercises to improve swallowing supervised by a therapist specially trained in neuromuscular disorders.

Musculoskeletal involvement

When there are musculoskeletal impairments and loss of motor functions:
– Periodically assess musculoskeletal deficits, loss of motor function and degree of disability.
– Radiographs to monitor the onset or worsening of scoliosis and long bone integrity (in children).
– Enhance muscle function through physical therapy.
– Prevent/minimize musculoskeletal impairment (contracture/deformity) with assistive equipment and devices to maintain proper posture. Use orthotics or surgery when needed.
– Screen for osteopenia/osteoporosis. Densitometry should be performed during the initial assessment and thereafter should be repeated at least every two years. Examine parameters of bone and mineral metabolism (calcium, phosphorus, PTH).

Genetic counseling

With the availability of molecular and genetic testing, it is possible to identify the mutations that are carried by a patient and his/her family. Once the genetical characterization of the index case has been performed, screening of at-risk family members is recommended. Genetic counseling should be provided to anyone who requests it.

Guidelines for genetic counseling:
– Perform molecular analyses to determine the pattern of mutations the index case carries.
– Determine the risk other family members have of carrying the identified mutations.
– Obtain the informed consent from all those who request genetic counseling; to do so you need to contact the genetics laboratory.
– When a family member has been determined to be a carrier of a mutation, a molecular analysis of his/her partner is recommended; assuming that he/she is a member of the general population, the risk of being a heterozygous carrier of a mutation in the gene that causes Pompe disease is approximately about 1 in 100.

After the molecular analysis has been performed, and depending upon the result, it will be necessary to determine the residual chance that the mutations will be transferred to the offspring, which in some cases may indicate a need for prenatal testing.

Treatment

Enzyme replacement therapy (ERT)

ERT is performed with infusions of alglucosidase α (human acid α-glucosidase produced by recombinant DNA in CHO cells). This treatment was first used in 2000 and clinical improvement was achieved in all of the patients who were treated [29]. The European Medicines Agency in 2006 and the Food and Drug Administration in 2010 gave approval for this treatment of late-onset Pompe disease.

Efficacy

Pompe disease is progressive, and the mortality rate is higher than in the general population, due mainly to muscle weakness and respiratory failure. For example, in the study Wokke et al [30], in which more than 50 patients with late-onset Pompe disease were followed, declines were observed in the strength of the limbs and in pulmonary function in just 12 months. Moreover, a study by Gung et al [31] in a large population of patients with untreated late-onset Pompe disease showed they had a survival rate that was less than that of the general population.

ERT treatment can stop or slow the progression of the disease. Indeed, many studies have been published that confirm the efficacy of ERT with alglucosidase α in the treatment of children with the classical phenotype of rapidly-evolving glycogen storage disease type II, especially for hypertrophic cardiomyopathy [32-35]. Experience in adults is more limited as there is great clinical variability, but there is sufficient evidence to substantiate that enzyme replacement therapy is effective. In the studies that have been published, the effects of ERT on skeletal muscle vary and depend on the degree of muscle involvement as well as the age of the patients [36]. In two clinical trials published by van Capelle et al [37] and van der Ploeg et al [38], in which 95 patients between the ages of 5 and 70 years with Pompe disease receiving ERT were followed up for three years, it was observed that in most cases there were benefits for the motor and respiratory functions and muscular strength. Additionally, in two observational studies published by Strothotte et al [39] and Bembi et al [40], ERT was administered for 1 year to 68 patients between the ages of 7 and 69 years who had Pompe disease; the benefits observed were consistent with the results found in clinical trials. Improvement or stabilization of disease has also been observed in patients with advanced stage Pompe disease who were severely disabled, as reflected in the study by Orlikowski et al [41]. The results of these studies suggest that the benefit of ERT is greater if it is started at an early stage, and in patients whose baseline clinical situation is in better condition [42,43].

Pretreatment evaluation and follow-up

Before beginning ERT it is necessary to perform a complete clinical and laboratory evaluation, similar to the diagnostic protocol described above. During follow-up it will be necessary to repeat some of the tests mentioned in order to monitor the efficacy of the ERT (Table V).

Dosage and initiation of the treatment

The decision on whether to initiate or delay treatment may have important implications for the course of the disease and the patient's quality of life.

The recommended dosage regimen of alglucosidase α is 20 mg/kg of body weight administered once every 2 weeks. As it is administered intravenously, a device such as a 'port-a-cath' may be implanted to make access easier. In some cases, 40 mg/kg doses have been given but at present it is not known whether varying the dose in accordance with the patient's clinical evolution may be beneficial.

No clinical studies have yet been conducted to show whether the treatment of asymptomatic patients can delay the onset of the symptoms of the disease. Nor is there yet sufficient evidence regarding whether or not to discontinue treatment in those patients for whom there are no objective benefits, nor regarding how much time to wait before discontinuing ERT.

That is, treatment should be given to cases that are:
- *Symptomatic*: when the diagnosis is confirmed.
- *Asymptomatic:* when they become symptomatic or when functional tests and/or neuroimaging (MRI) show a decline.

According to the experts who met in order to produce this guide there is insufficient evidence to support withdrawal of enzyme replacement therapy, although it may be reasonable for it to be withdrawn in the case of serious adverse events that cannot be controlled, severe comorbidity that limits the patient's life expectancy or if the patient should decide so.

The possibility of administering treatment to patients in their own homes exists and it is important to highlight the fact that patients can benefit greatly if treated at home [44].

Therapeutic objectives

As yet there is no international consensus regarding the objectives that should be sought by treating patients who have late-onset Pompe disease with ERT, but at the very least they should be the following:
- Stabilize or improve respiratory function (reduce or eliminate the need for mechanical ventilation).
- Stabilize or improve motor function, and prevent the onset of motor symptoms in asymptomatic patients.

Table V. Assessment protocol prior to initiation of enzyme replacement treatment and follow-up evaluations.

Prior assessment	Muscle assessment
	Manual assessment (MRC scale) of muscle strength
	Spirometry
	Forced vital capacity in sitting and lying supine positions
	Maximal expiratory pressure / Maximal inspiratory pressure
	Polysomnography and/or nocturnal oximetry (if available)
	Blood biochemistry analysis (transaminases, LDH, creatine kinase)
	Chest X-ray
	Anti-alglucosidase α and glucose tetrasaccharide antibodies (if available)
	Assessment scales
	Functional mobility scales: from lying supine to standing, going up and down four steps and global scales (Walton-Gardner-Medween)
	Timed functional tests: 6-minute walk test; 10-meter walk test, going up and down four steps, time to standing from lying supine and sitting positions
	Disability scales, such as Rotterdam Handicap Scale [52]
	Pain scales such as visual analog scales (VAS)
	Quality of life scales, such as the short form (SF-36) Health Survey
Follow-up evaluations	Muscle testing
	Manual assessment (MRC scale) of muscle strength
	Spirometry
	Forced vital capacity in sitting and lying supine positions
	Assessment scales
	Timed functional test and mobility scales: 6-minute walk test

MRC: Medical Research Council.

- Improve the nutritional status of the patient.
- Improve the patient's quality of life.
- Prevent or delay the onset of complications. In younger patients, attention should be paid to motor development and growth.

Safety

In general, use of ERT is safe but patients under treatment should be monitored for adverse effects. Fever and anaphylactic reactions may occur at the time of the infusion or within hours of it [33,34,38]. These events should be treated in the usual manner with antihistamines, corticosteroids and adrenaline, which should be at hand before proceeding with the ERT infusions.

In a recent randomized, double blind, placebo-controlled study during which patients with late-onset Pompe disease [38] who received ERT were followed for 78 weeks, the following safety outcomes were found:

- The frequency of adverse events and serious adverse events was similar in the two groups. Most of the adverse events were mild to moderate in intensity, and not considered to be related to the ERT. They were dealt with without need for the withdrawal of ERT. The most common adverse events (falls, nasopharyngitis and headache) were similar in both groups.
- 5-8% of the patients treated with alglucosidase α had allergic reactions with symptoms such as urticaria, flushing, hyperhidrosis, chest discomfort, vomiting and increased blood pressure. Of the 60 patients receiving ERT, two dropped out because of this. These reactions were not observed in the placebo group, but one of the patients in the placebo group withdrew because of headache.
- All of the patients in the group that received ERT developed anti-alglucosidase α HGPI antibodies within a short period (median time was 4 weeks) and in 31% inhibition of enzyme uptake was found. Nonetheless, inhibition of enzyme activity was not detected in any of these patients.

Other treatment options

The future looks promising for the treatment of Pompe disease and it seems the way forward will lie in gene therapy. Studies in mice have used viral vectors to replace the defective acid α-glucosidase gene although no clinical studies have yet been conducted in humans. A phase 2 co-administration study of chaperone AT2220 together with ERT is underway too [45].

It is also important to consider aspects such as diet and exercise, as recommended in the studies of Bembi et al [46] and Slonim et al [47] in which the natural course of late-onset Pompe disease cases improved in two cases using just nutrition therapy and exercise.

Psychological support for patients and their families

When Pompe disease is diagnosed in a patient, the

disease affects the entire family who will now need to become involved in caring for the patient. In some cases, this can be a terrible experience although it can also be very enriching for the family if they participate actively and jointly when the time comes to managing such a difficult situation. To be able to deal with things, it is important that both the patient and the family contact some organization of persons affected by the disease to request help. The most relevant ones are: the International Pompe Association [48], the Spanish Association of People with Glycogenosis [49], the United Pompe Foundation [50], and the Association for Glycogen Storage Disease UK – Pompe Disease Group [51].

People suffering from the disease and their families may require individual or family psychological counseling to accept the disease.

Psychological support programs are available at some of the centers for the treatment of Pompe disease in which the ERT is administered to help deal with the difficulties that may arise as a result of treatment, as it is of utmost importance for ERT to be well accepted in order to improve the prognosis of the patients.

Key conclusions and recommendations

- When faced with a history or clinical findings suggestive of Pompe disease (limb-girdle, especially pelvic, weakness, with or without respiratory symptoms), the patient should be referred immediately to specialists. Multidisciplinary monitoring of the patient is necessary and beginning treatment early can markedly improve their prognosis (level of evidence 3-4, grade of recommendation D).
- Using the analysis of α-glucosidase activity with dried blood spots technique (DBS) is an essential first step in the diagnosis of Pompe disease (level of evidence 1, grade of recommendation A).
- To confirm the diagnosis of Pompe disease, an assay of the enzyme activity in isolated lymphocytes in a liquid sample or mutation analysis of the α-glucosidase gene should be performed (level of evidence 1, grade of recommendation A).
- As for the genetic study, there is no justification for a population study in pairs of mutation carriers, although in the right context it can be very useful (level of evidence 2, grade of recommendation B).
- Although experience with enzyme replacement therapy in late-onset Pompe disease is limited, given that it is a rare disease with great clinical variability, there is sufficient evidence to substantiate that ERT is effective for improving or stabilizing motor and respiratory functions (level of evidence 1, grade of recommendation B) [38].
- ERT should be initiated as soon as symptoms attributable to Pompe disease appear (level of evidence 3, grade of recommendation D).
- There is insufficient evidence to support withdrawal of ERT, but it is reasonable for it to be withdrawn if: it is the patient's own desire that it should be, there are serious adverse events that cannot be controlled or severe comorbidity that limits the patient's life expectancy (level of evidence 4, grade of recommendation D).
- Nutritional intervention and aerobic exercise can improve motor function in patients (level of evidence 3, grade of recommendation D) [47].

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Guía clínica de la enfermedad de Pompe de inicio tardío

Resumen. Hasta 2006, la enfermedad de Pompe o glucogenosis tipo II era una enfermedad incurable y con tratamiento meramente paliativo. El desarrollo de la terapia de sustitución con la enzima alfa-glucosidasa recombinante humana ha constituido el primer tratamiento específico para esta enfermedad. El objetivo de esta guía es servir de referencia en el manejo de la variedad de inicio tardío de la enfermedad de Pompe, es decir, la que aparece después del primer año de vida. En la guía, un grupo de expertos españoles hace recomendaciones específicas en cuanto a diagnóstico, seguimiento y tratamiento de esta enfermedad. En cuanto al diagnóstico, el método de la muestra en sangre seca es imprescindible como primer paso para el diagnóstico de la enfermedad de Pompe, y el diagnóstico de confirmación de la enfermedad de Pompe debe realizarse mediante un estudio de la actividad enzimática en muestra líquida en linfocitos aislados o mediante el análisis mutacional del gen de la alfa-glucosidasa. En cuanto al tratamiento de la enfermedad con terapia de sustitución enzimática, los expertos afirman que es eficaz en la mejoría o estabilización de la función motora y pulmonar, y debe iniciarse cuando aparezcan los síntomas atribuibles a la enfermedad de Pompe.

Palabras clave. Alfa-glucosidasa. Análisis mutacional. Enfermedad de Pompe. Inicio tardío. Muestra en sangre seca (DBS). Terapia de sustitución enzimática.