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VIEW AND REVIEW

Guidelines for the diagnosis, treatment and clinical monitoring of patients with juvenile and adult Pompe disease

Diretriz para o diagnóstico, tratamento e acompanhamento clínico de pacientes com doença de Pompe juvenil e do adulto

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ABSTRACT

Pompe disease (PD) is a potentially lethal illness involving irreversible muscle damage resulting from glycogen storage in muscle fiber and activation of autophagic pathways. A promising therapeutic perspective for PD is enzyme replacement therapy (ERT) with the human recombinant enzyme acid alpha-glucosidase (Myozyme®). The need to organize a diagnostic flowchart, systematize clinical follow-up, and establish new therapeutic recommendations has become vital, as ERT ensures greater patient longevity. A task force of experienced clinicians outlined a protocol for diagnosis, monitoring, treatment, genetic counseling, and rehabilitation for PD patients. The study was conducted under the coordination of REBREPOM, the Brazilian Network for Studies of PD. The meeting of these experts took place in October 2013, at L'Hotel Port Bay in São Paulo, Brazil. In August 2014, the text was reassessed and updated. Given the rarity of PD and limited high-impact publications, experts submitted their views.

Keywords: Pompe disease, glycogen storage disease type II, acid alpha-glucosidase, muscular weakness, dyspnea, GAA gene, rhGAA.

RESUMO

A doença de Pompe (DP) é uma doença grave, potencialmente letal, devida ao depósito de glicogênio na fibra muscular e ativação de vias autofágicas. Tratamento promissor para a DP é a reposição enzimática com a enzima recombinante humana alfa-glicosidase ácida (*rhAGA* - Myozyme®). A necessidade de organizar uma propedêutica diagnóstica, sistematizar o seguimento clínico e sedimentar as novas recomendações terapêuticas tornaram-se vitais à medida que o tratamento permite uma maior longevidade aos pacientes. Uma força-tarefa de clínicos experientes no manejo da DP foi constituída para elaborar um protocolo para o diagnóstico, acompanhamento clínico, tratamento, aconselhamento genético, entre outras considerações voltadas ao paciente adulto. O estudo foi realizado sob a coordenação da Rede Brasileira de Estudos da Doença de Pompe (REBREPOM). Diante da raridade da DP e escassez de trabalhos de alto impacto de evidência científica, os especialistas emitiram suas opiniões.

Palavras-chave: doença de Pompe, doença de depósito de glicogênio tipo II, alfa-glicosidade ácida, debilidade muscular, dispneia, gene GAA, GAA recombinante humana.

DATA COLLECTION

This study began in 2013 with a web search on the databases Medline, Embase and LILACS using the following keywords: "Glycogen Storage Disease Type II" [MeSH] OR "Lysosomal Storage Diseases" [MeSH] OR "Pompe Disease" [MeSH] OR "Enzymatic Replacement Therapy" [MeSH]. We obtained 255 studies, 123 for childhood onset

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(< 18 years old) Pompe Disease (PD) and 132 for adult onset PD. We then selected studies based on their strength of recommendation and quality of evidence. In August 2014, a new search identified 329 studies published between the years 2010 and 2014.

Strength of recommendation and quality of evidence: A. experimental studies or strong observational studies (randomized);B. experimental studies or other observational studies (case-control); C. Case reports (uncontrolled studies); D. expert opinion without critical evaluation, based on consensus, physiological studies or animal models.

PD DEFINITION

Pompe disease (PD) (OMIM # 232300), also known as glycogen storage disease type II, is a rare lysosomal storage disease classified as an inborn error of metabolism[1]. It is caused by partial or complete deficiency in the activity of the acid alpha-glucosidase enzyme (GAA) (EC 3.2.1.20), which is essential for the degradation of lysosomal glycogen into glucose. This deficiency causes a progressive accumulation of glycogen in the cells of various tissues, manifesting in multisystem form, predominantly in the skeletal, cardiac and smooth muscle systems[1].

PD has been defined as a low/abnormal activity of the GAA enzyme in asymptomatic or symptomatic individuals and/or presence of two pathogenic mutations in the *GAA* gene[2] (B).

EPIDEMIOLOGY

The frequency of PD is quite variable (Table1). Recently, through a blind analysis of 100,000 samples obtained from neonatal screening through mass tandem spectrometry, Scott et al.[3] (B) identified, among other lysosomal diseases (Fabry and mucopolysaccharidosis type 1 - MPS I), an incidence of PD about 1/27,800 of the newborns.

Table 1. Pompe disease incidence in different populations.

Population (Year)	Incidence	Reference
Afro-Americans (2001)	1: 14,000	1
Dutch (1999)	1: 40,000 combined 1: 138,000 early onset 1: 57,000 adults	4
Americans (1998)	1: 40,000 combined	5
European Descendents (1998)	1:100,000 early onset 1: 60,000 adults	5
Australia (1999)	1: 145,000	6
Portugal (2004)	1: 600,000	7
Taiwan (2014)*	1:18.221 combined 1:52.538 early onset 1:27.866 late onset	8

*neonatal screening.

On the other hand, a study conducted in 104 muscle biopsies from asymptomatic or oligosymptomatic (fatigue, cramps, myalgia) patients, with increased serum CK, normal physical examination and no statin exposure, PD in juvenile and adults (PDJ-A) was identified in 3.8% of patients[4] (C). Werneck et al.[5], in a particular study of symptomatic cases, reviewed 4,500 muscle biopsies performed over a period of 33 years in a reference center for neuromuscular diseases in Brazil and identified 19 cases of PD, 10 cases of early onset PD and 9 cases of PDJ-A (C).

PATHOPHYSIOLOGY

PD is an autosomal recessive disease caused by pathogenic mutations in both copies of the gene that encodes the enzyme *GAA*. Hundreds of mutations have been identified in the *GAA* gene (*http://www.pompecenter.nl/*).

PD severity and age of symptom onset are related to the level of residual activity of the GAA enzyme. Early onset infantile PD results from a complete deficiency of the enzyme (activity < 1%), while late onset PD (juvenile or adult) results from partial deficiency of GAA (1-30%). Onset may occur as early in childhood or as late as at the sixth decade of life[6,7] (B).

The cause of PD is the progressive accumulation of intralysosomal glycogen due to the inability of the cell to breakdown the lysosomal glycogen into glucose. As a result, lysosomal membranes rupture, causing leakage of hydrolytic material into the cytoplasm with impairment of the muscle contractile unit[1]. There is also saturation of autophagic pathways during the pathophysiological process[8] (C).

SYMPTOMS AND SIGNS OF JUVENILE AND ADULT POMPE DISEASE (TABLE2)

The clinical manifestations vary according to the patient's age, the rate of disease progression and the extent of organ involvement, and may result in irreversible motor impairment[9,10] (B). The most common manifestation in adults is progressive muscle weakness simulating the muscular dystrophies. Most patients present weakness of the proximal and axial musculature, especially in the lower limbs[14,15] (C). Weakness of the paraspinal muscles of the lower back, weak and protruding abdominal muscles, weakness of facial muscles and eyelid ptosis and tongue paralysis reinforce the clinical suspicion[11,12,13].

The presence of dysphonia and dysphagia reflects the disease's bulbar impairment[14], and involvement of the auditory system has also been reported[15].

GUIDED PHYSICAL EXAMINATION

The physical examination in PDJ-A should focus on the muscular and respiratory systems.

Pain and fatigue are regularly reported symptoms[16]. Diaphragm muscle weakness occurs early on in PD, and may precede limb or axial muscle weakness[17] (B).

In a patient that is asymptomatic or has muscle fatigue, the following signs and symptoms may be seen in PDJ-A:

- compensatory rotation of the body to rise from the ground[11] (C);
- morning headache; narcolepsy[17] (C);
- myopathy with myotonic paroxystic discharges (as seen in EMG) without clinical myotonia[18] (C);
- CK levels that do not exceed 15 times the normal value[4] (C);
- increased transaminases without liver disease in asymptomatic or oligosymptomatic individuals[19] (C);
- vacuolar myopathy assessed by muscular biopsy[5] (C);
- MRI imaging with evidence of muscle atrophy or diffusion abnormalities during the process of fat suppression in the posterior thigh, abdominal or paravertebral muscles[20] (C);
- cardiac arrhythmia associated with skeletal muscle weakness[21] (C);
- loss or rigidity of aortic compliance and hypertension[22] (C);
- idiopathic stroke with middle cerebral artery aneurysms[23] (C);
- post-pubertal adolescent or adult idiopathic scoliosis[24] (C);
- rigid spine syndrome[25](C).

Table 2. Summary of the main clinical features of adults with Pompe disease[2,8,9].

Organ or system	Clinical features
Skeletal muscle	Weakness of the pelvic and shoulder girdles Myalgia Exercise intolerance and fatigue Axial muscle weakness: abdominal and lumbar paraspinal muscles Contractures and deformities ("idiopathic" rigid spine)
Other muscles (facial, oral)	Tongue weakness Macroglossia Eyelid ptosis Dysphonia Dysphagia Difficulty in chewing
Lung	Dyspnea on exertion Orthopnea Acute respiratory failure Central and obstructive sleep apnea Sleep disorder - morning headache
Other systems	Hepatomegaly Ectasia of the cerebral arteries with vascular aneurysm Wolf-Parkinson - White syndrome Postprandial pain in the elderly Chronic diarrhea Hyperlordosis and/or scoliosis
Outcomes	Adults with PD have a respiratory disturbance often before the muscle weakness Slow progression of motor weakness Disease progression with stability for long periods Patients with early respiratory insufficiency may have a worse prognosis

DIFFERENTIAL DIAGNOSIS

Early involvement of respiratory muscles anticipating muscle weakness may differentiate PDJ-A from other neuromuscular diseases[17].

Table 3 lists the diseases considered in the differential diagnosis of PDJ-A.

DIAGNOSTIC LABORATORY METHODS FOR JUVENILE AND ADULT POMPE DISEASE

Dry blood spot on filter paper as a screening test for PD

The introduction of the dry blood spot (DBS) test on filter paper into clinical practice provided a simple and reliable laboratory method for screening patients with suspicion of PD[26,27] (Table 4).

Whenever the suspicion of PD persists, the test should be repeated, and additional diagnostic methods should be employed (Table 4). As all screening tests, suspected cases require a confirmation by at least one diagnostic test[26,27] (B, C). DBS pre-analytical problems may result in false-negative and/or false positive screening results[26].

Laboratory diagnosis for childhood and adult PD

Upon a positive DBS screening test for PD, additional diagnostic evidence should be obtained by measuring the

Table 3. Differential diagnosis in Pompe disease[2,a] www.musclegenetable.org

Neuromuscular disorder	Disorder
Muscular dystrophies	Girdle muscular dystrophies
	Duchenne e Becker muscular dystrophies
	Miofibrilar myopathy
	Myotonic Distrophy type 2
Inflammatory myopathies	Polymyositis
Congenital myopathies[b]	Nemaline myopathy
	Central Core or Multiminicore myopathy
	Centronuclear myopathy
	Danon disease
	X-linked myopathy with na excesso f autophagy
Metabolics myopathies	Glycogen debranching enzyme deficiency (Glycogenosis Type IIIa ou IIIb – Cori or Forbe disease)
	Glycogen branching enzyme deficiency (Glycogenosis Type IV – Andersen Disease)
	McArdle syndrome
	Mitocondrial myopathies[c]
Motor neuron disease	Spinal mucular atrophy Types 2 e 3
Neuromuscular junction disease	Miastenia gravis Congenital myastenic syndromes[c]

[a]refers primarily to the late onset PD form; [b]congenital myopathies can simulate either early onset as late onset PD; [c]refers primarily to the early onset PD form.

Table 4. Recommendations for diagnostic tests in Pompe disease in adults[26].

Screening Test – DBS – "*dried blood spot*" on filter paper to perform enzymatic activity analysis of acid α-glucosidase (GAA)[a,b]
"Gold standard" Diagnostic Test – in fibroblasts or muscle tissue for acid α-glucosidase (GAA) enzymatic assay
Diagnostic Test – molecular analysis of the *GAA* gene[b]
Diagnostic Test in DBS – GAA activity in lymphocytes and/or leucocytes

[a] In clinical practice, the definitive diagnosis of Pompe disease is now being based on the molecular analysis of the *GAA* gene for the presence of two pathogenic allelic mutations (www.pompecenter.nl); [b]Genetic variants of the *GAA* gene [c. (1726A; 2065A)] have been identified, especially in Asian populations; the combination with a pathogenic *GAA* allelic pathogenic mutation reduces the GAA enzyme activity on enzymatic assays specially from filter papers, which leads to false positives results considering neonatal screening programs. Such individuals are not diagnosed with PD and are instead classified as being pseudo-deficient individuals for the GAA enzyme.

amount of GAA activity in leukocytes or fibroblasts[26] and/or by conducting *GAA* genotyping in search of two pathogenic *GAA* mutations[2] (Table 4).

Whenever there is any doubt in the DBS test and clinical suspicion persists, patients with symptoms suggestive of PD should have their GAA activity measured once again by the same laboratory that performed the first analysis. If the patient is negative for the GAA enzyme assay in leukocytes and the possibility of PD persists, diagnosis should proceed with at least one of the following three options:

a) DNA analysis searching for pathogenic mutations in the *GAA* gene[2]; or

b) Muscle biopsy evaluation, to assess the presence of abnormal accumulation of glycogen with vacuolar myopathy[5,29] (B), although not specific for PD; or

c) Fibroblast culture from skin biopsy to test for *GAA* activity[26].

GENETIC ASPECTS OF JUVENILE AND ADULT POMPE DISEASE PATIENTS – GENOTYPE-PHENOTYPE CORRELATION AND CRIM STATUS

The enzymatic deficiency in PD is caused by pathogenic mutations in both alleles of the *GAA* gene. Mutations can be similar (homozygote); or, different (compound heterozygote); however, both within the *GAA* gene. The most common mutation observed in PDJ-A patients, including Brazilians, is the intronic alteration c.-32-13 T > G (IVS1-13T > G), which is observed in more than two-thirds of the patients worldwide[7,30]. The type and combination of these mutations will determine the amount of residual GAA activity in the cells[6,7].

The combination of two severe mutations leads to a complete lack of GAA protein and, as a consequence, an extremely low residual GAA activity (< 1%); such genotype is associated with the severe early onset PD[31]. From an immunological point of view, these individuals are classified as CRIM (*Cross Reactive Immunological Material*) negative patients. CRIM negative individuals who undergo ERT with GAA (*rhGAA enzyme*) may have severe reactions to the infusion, as well as the production of high titers of IgG antibodies[32]. (B)

On the other hand, any other combination of mutations, being at least one of then considered a "milder" mutation, such as the classic c. -32-13 T > G, enzyme production will occur, even if abnormally, resulting in different levels of residual GAA activity of up to 30% of the normal value[6,7]. Patients with at least one mild mutation constitute most cases of juvenile and late-onset PD and present a clinical phenotype with a slower progression[1,7]. From an immunological standpoint, these patients are classified as CRIM positive[31], and generally, will probably not be prone either to severe adverse reactions to Enzyme Replacement Therapy (ERT) with the *rhGAA* enzyme or sustain high titers of antibodies[33] (B).

ENZYME REPLACEMENT THERAPY IN PATIENTS WITH CHILDHOOD AND ADULT POMPE DISEASE

Until recently, treatment for PD consisted only in palliative care. In a natural history study of 255 patients with DPJ-A, disease severity assessed by the need for a wheelchair or dependence on mechanical ventilation showed that progression to wheelchair use increased, on average, 13% each year in patients without ERT treatment[34] (B).

In 2007, the commercial use of the *rhGAA* enzyme was approved for early onset PD patients; and, in 2010, for the late-onset PD presentation. In the 18-month clinical trial conducted with the *rhGAA* enzyme in the late-onset PD form, there was an increase in the six minute walk test as well as stabilization of their pulmonary function[35] (A).

The goals of *rhGAA* enzyme therapy depend on the stage of disease progression[35,36] (B), and include:

- To slow down, stabilize or reverse disease progression;
- To reduce comorbidities and increase survival;
- To improve mobility, preserve motor function, delay the need for walking assistance, and promote motor gains;
- To improve or maintain respiratory function, thus preventing the need for respiratory assistance;
- To improve or preserve patient independence and quality of life.

A systematic review[37] of the clinical and therapeutic outcomes of ERT with the *rhGAA* enzyme after one year of treatment in 251 patients with the PD-A presentation and 27 patients with juvenile PD yielded the following findings:

- six-minute walk test: 78% increased the distance covered, 8% maintained the same distance, and 4% decreased the distance;
- Motor Performance: 10% improved, one bedridden patient was able to sit up, three patients in wheelchairs

were able to walk a few times a day, and three patients no longer required wheelchairs;
- Forced Vital Capacity (FVC) (127 patients): 53% improved and 33% worsened;
- Ventilatory support (58 patients): 70% improved.

The delay between the first symptoms of the disease, the definitive diagnosis of DPJ-A, and the beginning of ERT, have shown an inverse relationship with the therapeutic prognosis and clinical outcomes desired[38].

Practical instructions for enzyme replacement therapy

Currently, there is only one commercially available product for ERT with the *rhGAA* enzyme for PD (Reg MS: 1.2543.0020.001-0.)

Regardless of the PD type, treatment with the *rhGAA* enzyme should be started at a reference hospital where it would be possible to intervene in the event of any adverse event related to the venous infusion[39]. It is also essential to inform the family about the goals of ERT, the treatment expectations based on the stage of the disease, and the guidelines for clinical follow-up and evaluation[28,40].

Health professionals should address the difficulty of predicting the response to long-term ERT treatment and prioritize factors that could potentially influence treatment response, such as respiratory function and muscle involvement. The multidisciplinary team should be instructed regarding these issues. We recommend training the nursing and pharmacy staff on the handling of the drug prior to the first infusion, and provide specific guidance to physicians and the infusion center staff. One should always record the occurrence of any adverse event, whether or not they are associated with ERT. The dose of *rhGAA* enzyme for ERT should follow the manufacturer's recommendations. The current standard dose of Myozyme® is a minimum four-hour infusion of 20mg/kg every 15 days.

While adverse events in patients with PDJ-A are considered rare (see Genotype-Phenotype correlation)[39], infusion-related reactions generally require medical intervention. These reactions are usually mild to moderate and respond positively to a reduction in infusion rate.

The most serious and rarely observed side effects of ERT with *rhGAA* are life-threatening anaphylactic reactions, serious allergic reactions and immune-mediated reactions. Such events are also rare in late-onset PD because patients are CRIM positive[32].

Inclusion and exclusion criteria for enzyme replacement therapy (Table 5)

The heterogeneity of symptoms and signs present in PD patients (Table 2), the intra-familial variability and different stages of PD have led to the characterization of different patient groups and created a clinical dilemma of when to put a patient on ERT with *rhGAA*. The groups currently are identified as newborns identified via newborn screening[8]; asymptomatic patients with or without clinical signs of the disease[41]; symptomatic PD patients[36] and patients with severe PD[9,10] (Table 5).

Table 5. Summary of recommendations for ERT treatment based on the stage and severity of Pompe disease.

Asymptomatic patients without objective clinical signs
Patients should be examined for proximal muscle weakness and lung function (Pompe registry recommendations, www.registrynxt.com/).
ERT should be considered if:
Symptoms appear
Appearance of proximal muscle weakness and/or > 10% drop in sitting-supine forced vital capacity
Asymptomatic patients with objective clinical signs
ERT should be considered if:
Patient is asymptomatic with muscle weakness detectable by directed examination
Typical vacuolar muscle biopsy
> 10% drop in sitting-supine forced vital capacity
Symptomatic patients
Enzyme replacement therapy should be considered if:
> 10% drop in sitting-supine forced vital capacity; or increased muscular weakness; with or without ventilatory support
Patient has difficulty conducting daily routine tasks
Severe patients
If the patient is confined to a wheelchair and using continuous invasive ventilation:
ERT is recommended for 01 year, followed by evaluations to assess therapy effectiveness
After 01 year of ERT, the multidisciplinary team will review the treatment case-by-case, especially for patients requiring continuous invasive ventilation
ERT will be continued if there is stabilization or improvement of severe signs and symptoms
ERT duration
Annual reassessment to review the effectiveness of treatment
Monitoring
Patients receiving enzyme replacement therapy should have IgG antibody levels monitored every 03 months for up to 02 years, and then annually (www.registrynxt.com)

ERT: enzyme replacement therapy.

In most cases of PDJ-A, the duration of *rhGAA* treatment is indefinite. Thus, the treatment goals, the timing of clinical evaluations, and quality of life studies (SF-36 - www.sf-36.org/), may support the multidisciplinary team in clinical management decisions[28,40,41]. It appears that major improvement of muscle strength and respiratory function with ERT is not common in patients with late-onset Pompe's disease[35]. The termination of ERT can be a very difficult task, and there is no consensus regarding this topic except on a case-by-case discussion. The involvement of family members in such decisions is very important[28,40] (Table 5).

Monitoring and laboratory tests for enzyme replacement therapy

PD patients on ERT with the rhGAA enzyme will make seroconversion in 95% of cases becoming IgG positive[39]. However, exceptionally high titers of persistent antibodies may occur and this can activate the complement cascade and neutralize the rhGAA enzyme[32]. In these circumstances, there is a decline of the therapeutic response to ERT (walking, lung function, SF-36) and adverse events associated to ERT may be observed[32] (B). Currently, immune modulation and immune suppression protocols, in an attempt to reduce neutralizing antibodies against *rhGAA*, have been successfully applied in infantile onset PD patients with high sustained IgG antibodies[42]. Patients with PDJ-A are CRIM-positive and therefore are less likely to have such serious immunological reactions[32]. The concentrations of IgG and IgE antibodies, tryptase and complement activation studies need to be monitored based on the Doctor's Guide to Clinical Management of Pompe Disease.

Hypersensitivity to the drug should be considered an absolute contraindication to the use of ERT with *rhGAA* enzyme.

Pregnancy, lactation and enzyme replacement therapy

Since the introduction of ERT, a growing number of women with metabolic diseases have been able to reach reproductive life and become pregnant. Pregnant women with Gaucher, Fabry and (more recently) Pompe disease, are creating a new clinical challenge for obstetricians[43,44].

Until 2014, two cases of pregnant women with PD receiving ERT have been published[44,45]. Recently, Karabul et al.[46] collected information on 52 women with PD-A and 125 pregnancies through a retrospective self-administered questionnaire sent to Pompe associations in England and Germany, as well as neuromuscular disease centers in Germany. Pregnant women undergoing ERT not exhibited a reduction in mobility and muscle function, and many asymptomatic patients experienced their first PD symptoms during pregnancy[51]. Many pregnant women also used wheelchairs intermittently. A decrease in lung function, as measured by spirometry, was common to all pregnant women, including those undergoing ERT. Nonetheless, the reported experiences were highly favorable to the use of ERT during pregnancy, anesthesia, postpartum, newborn health, lactation and recovery of pre-pregnancy clinical status[46]. FDA classification/pregnancy category B (http://www.accessdata.fda.gov).

Pregnant women with neuromuscular diseases and vital capacity < 1l (normal reference = 4.5l) should be warned of the high risk of complications during pregnancy and childbirth. In case of maternal hypoxia with O_2 saturation under 85%, the rate of live births is only 12%. The recommendation for pregnant women with PD is a cesarean delivery under local instead of general anesthesia[47].

MULTIDISCIPLINARY CLINICAL MONITORING

Due to the predominance of muscular signs and symptoms, PDJ-A is primarily a neuromuscular disease. Thus, the neurologist's role is crucial in coordinating the clinical decisions made by the professional health team[2,28,40].

The ICD-10 classification (E74.0) may not accurately describe the functional impairment and disability associated with PD, since these patients vary in their degree of functionality. The International Classification of Functioning, Disability and Health (ICF)[48] provides more meaningful information and data for clinical purposes (Table 6).

A study of 210 adults with PD using the Quality of Life Scale (SF-36) survey[34] highlights the impact of the disease on patients' ability to work, perform household activities and move independently outside of their home. Progressive disability also increases the dependence of family members and other supportive care in the management of PD patients.

We recommend using disability scales (the Rotterdam study), visual analog scales for measuring pain, and the SF-36.

Table 6. Classification of functioning, disability and health (ICF) for adult Pompe disease (2003). www.who.int/classification/icf

Code	Domain
b134	Sleep functions
b3100	Voice production
b445; s430	Respiratory muscle functions; structure of the respiratory tract
b455	Exercise tolerance functions
b510	Food intake functions
b525	Defection functions
b530	Weight maintenance functions
b730	Muscle strength functions
d230	Performing daily routines
d450	Walking
d460	Moving through different locations
d598	Self-care
d640	Performing household chores
e120	Products and technologies to facilitate mobility and/or transport the person indoors and outdoors

Functional rehabilitation of skeletal muscles

Skeletal muscle involvement in PD is characterized by progressive weakness, poor posture and compensatory movement patterns. Table 7 lists the main recommendations for patients with PDJ-A regarding the maintenance of functional muscle activity.

The assessment of skeletal muscle function, strength and structure should include:

- Timed functional tests and mobility scales: 6-minute walk test; 4-step ascent and descent staircase test[40,49];
- Manual or quantified evaluation of muscles strength (MRC scale)[49];
- Evaluation of tongue strength[13];
- Magnetic resonance imaging of the skeletal muscle, including tongue, paraspinal and thighs[20].

Active physical activity

Recent evidence shows that people with carbohydrate processing disorders can benefit from light exercise[50] (C). People who are physically fit are better able to use alternative sources of fuel for energy. Excessive strain in PDJ-A can cause muscle injuries; therefore, all exercise programs should be supervised by a professional familiar with PD (Table 6).

Therapeutic exercise should start lightly, be interspersed with rest periods, and follow a gradual increase in intensity until it reaches 60-75% of maximum effort in three to five days per week[50] (B). Strenuous or eccentric physical therapy exercises should be avoided, especially in proximal muscles, flexors and abductors of the lower limbs (Nascimento, Siqueira and Barone, personal observation, 2014).

Optimization of the biomechanical advantages of movement:

- Provide positioning and support to increase biomechanical advantage;
- Save energy;
- Optimize the effects of gravity;
- Consider positions that improve the muscle length-tension relationship
- Minimize muscle contracture.

Prevention of secondary musculoskeletal deficits (Table 7)

Secondary musculoskeletal impairments can be prevented by following the principles of biomechanics to counteract deforming forces. This is done by applying light pressure, stretching, practicing posture correction, performing orthotic interventions, and using seating and support systems[51].

Recent studies show that the mobilization and utilization of fat and carbohydrates in skeletal muscles during exercise are normal in PD. In fact, the reduction in exercise capacity results from muscle weakness and wasting and not from a reduction of muscle glycogenolysis, even with ERT therapy[51] (B).

Pulmonology

Respiratory failure is a major cause of mortality and morbidity in PDJ-A[10,11,17] (B). Approximately 60% of individuals with PDJ-A show a slight decrease in vital capacity (less than 80% of normal) and 30-40% show a moderate decrease (less than 60% of normal)[10,11] (C). Observational studies have shown average annual declines in FVC of 1.7% to 4.6%[11] (B).

As PDJ-A progresses, muscles weaken and lung volume is reduced. Consequently, cough can become harmful,

Table 7. Summary of recommendations for the evaluation and rehabilitation of the musculoskeletal system in juvenile and adult patients with Pompe disease.

Include the patient in the International Pompe Registry (www.registrynxt.com/)
Physical examination and evaluations
Evaluation by a cardiologist and pulmonologist prior to physical therapy and aerobic exercise
Baseline 6-minute walk test (*ATM Statement, 2002; www.registrynxt.com*).
Annual densitometry (DEXA) (even for patients in wheelchairs)
PD patients with reduced bone density: assessment by specific tests and endocrinologist
Walking assistance equipment to reduce falls
Physical/occupational therapy
Physical therapy program including walking, treadmill, bicycle, hydrotherapy, swimming, muscle strengthening for neuromuscular diseases;
Avoid extreme exercise, excessive fatigue and immobility
Emphasis on aerobic exercises
Incorporate into daily functional activities
Instruct the patient to monitor heart rate and breathing during exercise
Daily exercise regime for the prevention of contractures
Managing contractures
Orthotic devices to prevent joint contractures with posture assessments while the patient is in the wheelchair and support for when he/she stands
Surgical intervention
Surgical intervention for scoliosis when the Cobb angle is between 30° and 40°
Vitamin and Mineral supplements
Vitamin D, calcium and bisphosphonates following the osteoporosis manual

blood-gas values become abnormal, and respiratory conditions may disrupt sleep[52,53].

The guidelines for monitoring and treating pulmonary aspects of PD include[52,53] (C):

- Clinical evaluation of respiratory status by a pulmonologist experienced in the clinical management of patients with neuromuscular diseases;
- Evaluation of pulmonary function and blood gas analysis at diagnosis, annually, at each medical visit, or as changes occur in the course of the disease;
- Update the immunization record, including influenza and pneumococcus;
- Frequent removal of secretions from the lung airways (cough devices, aspiration);
- Assess the use of the ***cough-assist*** device and train/educate patients and families about its use and muscle inhalation techniques;
- Evaluation of respiratory function during sleep if the patient feels sleepy during the day, presents with unexplained fatigue, sleep apnea, morning headaches, or when his/her vital capacity falls below 40-50% of normal;
- Treat sleep disorders with positive airway pressure (CPAP) or with non-invasive nocturnal ventilation (BiPAP);
- In the absence of sleep studies, consider BiPAP ventilation if P_{CO2} is ≥ 45 mm Hg, or supine forced vital capacity < 50% of predicted, or negative forced inspiration < 60 cm H_2O, or oxygen saturation is < 88% for more than 05 continuous minutes during sleep;
- Aggressive treatment against all lung infections, and concomitant diseases sucah as asthma and cardiomyopathy;
- Consider enzyme replacement therapy with recombinant human GAA.

  For pregnant PD women clinical caution is vital regarding the pulmonary and muscle functions (see 7.4 Pregnancy, lactation and enzyme replacement therapy).

Nutritional and gastrointestinal evaluation and treatment

PD patients have difficulty swallowing and eating. Factors contributing to this difficulty include facial hypotonia, macroglossia, weakened tongue muscles, and impairment of oral movements. Patients have difficulty dealing with saliva and secretions usually accumulate on the vocal cords, which can also lead to respiratory complications. They experience fatigue of the jaw muscles as well as difficulty chewing and eating certain foods. For these reasons, patients with PD often consume low amounts of vitamins, minerals and energy, resulting in malnutrition and the compensatory use of muscle proteins, in addition to increased risk of microaspirations and aspiration pneumonia by vomiting or regurgitation. Also, nutritional problems arising from gastrointestinal muscle weakness may also be present, including dysphagia, gastroesophageal reflux, gastroparesis, and decreased bowel movements leading to constipation.

Patients should be assisted by a group of professionals that includes: a speech therapist, a stomal therapist, a psychologist, a dietitian and a nutrition specialist (preferably with experience in metabolic diseases) to ensure proper nutritional care. Diets and food consistency should be reassessed regularly.

For patients with PDJ-A, the main goal of the diet - other than adequate nutrition - is to control glycogen accumulation and the processing of amino acids. We recommend a high protein diet (20-25% of total energy intake from protein, 30-35% from carbohydrates and 35-40% from lipids), with special attention to vitamins and minerals, and modification of food consistency. Diets rich in protein and/or L-alanine and low in carbohydrates have shown positive results in PDJ-A. Supplement with 1.4 g of L-Alanine up to 04 times a day is indicated if the recommended protein content associated with 4% (500 ml) of branched-chain amino acids cannot be met. Results are optimized with training and physical activity. Body composition measurements include body mass index (kg/m^2) calculation, waist circumference and/or plicometry and Dual-energy X-ray absorptiometry (DXA).

Approaches to gastrointestinal problems include postural swallowing techniques, swallowing maneuvers to improve facial muscle coordination (supraglottic, Mendelsohn maneuver), environmental modifications, and oral sensory awareness techniques. The use of a feeding tube (nasal tube, gastrostomy or gastrojejunostomy tube) should also be considered.

Swallowing

In PD patients with dysphagia, positive results have been obtained with a soft diet consisting of purees and similar preparations, and including the use of thickeners.

Percutaneous endoscopic gastrostomy (PEG) is a surgical endoscopic procedure that aims to provide extended food access for patients with an intact and functional gastrointestinal tract, but who are unable to maintain adequate oral energy intake[54]. PEG is indicated for PDJ-A patients with severe dysphagia, aspiration risk, weight loss (>10% in one year) and FVC < 40%[54]. The Brazilian Ministry of Health established (***Portaria GM/MS No. 343e No. 120***) mechanisms for the implementation of assistance centers and high complexity reference centers for nutritional therapy as part of SUS (***Sistema Único de Saúde***), and established their technical and operational requirements (procedure code 98.003.02-0). Gastrostomy involves a laparotomy and often general anesthesia, which limits its use in patients with severe PDJ-A (see ***Anesthesia/Surgery***). The main indication of PEG in daily clinical practice is for long-term enteral nutrition for patients with dysphagia[54].

Anesthesia/surgery

The medical staff must carefully attend to a series of considerations when indicating surgery to patients with PD, because the increase risk of complications involving anesthesia[55] (B/C).

Patients with neuromuscular diseases due to metabolic causes may have a higher risk of adverse events to general anesthetics, especially the combination of halothane and succinylcholine[55].

The following guidelines are recommended for surgery procedures in PDJ-A:

- Conduct anesthetic procedures only when necessary;
- Consolidate all surgical procedures requiring anesthesia to reduce the risk of exposure to the anesthetic;
- Avoid tracheal intubation and, if indicated, make sure it is performed by an experienced professional;
- Conduct rigorous intraoperative supervision;
- Use inhalation agents in non-severe patients;
- Avoid depolarizing agents due to the risk of severe hyperkalemia;
- Monitor circulating fluid volume;
- Whenever possible, perform surgery in centers with professionals experienced with PD.

Family history and genetic counseling

PD is an autosomal recessive disease caused by pathogenic mutations in both alleles of the *GAA* gene[1,7]. Parents of individuals with PD are healthy obligatory heterozygotes with a risk of PD recurrence in their future offspring of approximately 25%. Therefore, once an individual is diagnosed with PD, it is essential for parents to receive genetic counseling. The diagnosis of an individual with PD justifies the active search of the disease among his/her siblings. Asymptomatic or mildly symptomatic cases are often identified due to the intrafamilial clinical variability observed between two siblings with PD. Laboratory screening and diagnostic methods are the same as for the index case (Table 4).

Individuals with PDJ-A have benefited from ERT, with increased survival rates. As a result, some of them may have families once they reach reproductive age, especially those who are mildly symptomatic or diagnosed with late PD. An individual with PD can have an affected child if his/her partner is heterozygous for mutations in the gene that causes the disease. Pregnant women with PD require intensive supervision (see *Pregnancy*).

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ERRATUM

Erratum

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The citation numbers and the references were modified, as shown below:

	should be		should be
9	4	35	30
10	5	36	31
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34	29		

Excluded references:
4 to 8 and 58.

New reference:

48. World Health Organization. International classification of functioning, disability and health. Geneva: World Health Organization; 2001.