The Brazilian Consensus on the Management of Pompe Disease

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The Brazilian Consensus on the Management of Pompe Disease was established through collaboration of all Brazilian physicians known to be treating patients with Pompe disease (PD) in Brazil. It was based on the clinical presentation of 7 cases of early-onset PD (EOPD) and 18 cases of late-onset PD (LOPD) presented to a working group in the city of Rio de Janeiro in 2007. Coordinated by the Brazilian Network for Studies in PD (ReBrPOM) with key objectives of enhancing understanding of the clinical heterogeneity, progression, and natural history of this severe and lethal genetic disease, as well as providing an overview of the Brazilian experience with enzyme replacement therapy with recombinant human acid alpha glucosidase (rhGAA; Myozyme; Genzyme, Cambridge, Massachusetts). This is not an exhaustive investigation of the issue, but rather preliminary guidelines to optimize the management of these patients under the care of the Brazilian public health care system (SUS-Brasil).

PD (MIM 232300), also known as glycogen storage disease type II or acid maltase deficiency, is rare, progressive, and, in its early form, often fatal.[1] The disease is inherited in an autosomal recessive fashion and is caused by a deficiency of the enzyme acid alpha-glucosidase (GAA; 3.2.1.20), which has an intralysosomal action and is responsible for releasing glucose units from glycogen. Glycogen buildup occurs within lysosomes of several tissues, particularly in skeletal and cardiac striated muscle cells in early-onset PD (EOPD), destroying the cells and compromising muscle fiber function. The disease may present in the first year of life, characterized mainly by hypertrophic cardiomyopathy and generalized muscular hypotonia, or after the first year through the sixth decade of life, with progressive proximal muscular weakness and respiratory complaints as the major symptoms.[2]

To date, no global studies have been published that can accurately determine the incidence of PD. Present incidence estimates are 1/138 000 births for EOPD and 1/57 000 births for late-onset PD (LOPD). The overall worldwide incidence of PD is estimated at 1/40 000. A significant ethnic influence has been identified, evidenced by the higher incidence of EOPD in African-Americans (1/14 000) and Chinese (1/40 000 to 1/50 000).[2]

Classification

The historical classification is based on age of onset, presence or absence of cardiomegaly, and rate of progression. Thus, manifestations appearing within the first 6 months of life with cardiomyopathy and rapid progression is considered the most severe form of the disease. In general, infants who present with onset of symptoms in the first year of life have cardiac impairment, although the severity of this manifestation is variable. On the other hand, patients with onset of symptoms after the first year of life have slight or no cardiac involvement.[2-7] Most patients with symptom onset after age 2 years have muscular impairment exclusively.[2,6,7]

In the present consensus, we adopted the classification system emphasizing the presence or not of cardiomegaly, disregarding the age of symptom onset, based on the significant differences in clinical and follow-up management of those patients presenting with cardiac involvement.[2-7] A continuum clinical spectrum in PD patients from a pathophysiologic standpoint has been considered and emphasized.

Clinical Presentation

EOPD

Symptoms may be present at birth or appear within the first few months of life (on average, by 4 months). The symptoms include cardiomyopathy (dilated or hypertrophic), hypotonia, and rapidly progressive muscular weakness, in conjunction

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CK	Creatinine kinase
CK-MB	Creatinine kinase MB isoenzyme
CRIM	Cross-reactive immunologic material
EOPD	Early-onset Pompe disease
ERT	Enzyme replacement therapy
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GAA	Acid alpha-glucosidase
LOPD	Late-onset Pompe disease
NIV	Noninvasive ventilation
PD	Pompe disease
PEDI-POMPE	Pediatric Evaluation Scale for Pompe Disease
rhGAA	Recombinant human acid alpha-glucosidase

with delayed motor milestones, followed by death from cardiorespiratory failure, usually by age 1 year.[7] Impairment of respiratory muscles (including abdominal and intercostal muscles and the diaphragm), leads to rapid-onset respiratory insufficiency. Swallowing difficulties are common, causing malnutrition, repeated aspiration pneumonia, and respiratory tract infections. Other common findings include macroglossia, hepatomegaly, hearing loss, osteopenia, and scoliosis.[7-10] Patients with EOPD develop cardiomyopathy secondary to the massive accumulation of glycogen within the cardiac muscles. They have biventricular hypertrophy, including hypertrophy of the ventricular septum, which can be present at birth or develop within the first year of life. Hypertrophy may result in left ventricular outflow tract obstruction and progress to dilated cardiomyopathy. Glycogen accumulation also affects the specialized conduction tissue cells and gross depolarization and repolarization patterns, resulting in characteristic eletrocardiographic changes, including shortened PR interval, increased QT dispersion, and enlarged QRS complexes.[3,11] The hypertrophic cardiomyopathy and conduction system abnormalities put these patients at risk for ventricular arrhythmias and sudden death.[12] Two natural history studies delineate the EOPD course. In the first study, which included 20 Dutch cases and 133 cases from the literature, the median age at symptom onset was 1.6 months in both groups, the median age at diagnosis was 5.3 months in the Dutch group and 4.5 months in the literature cases, and the median age at death was 7.7 months and 6.0 months, respectively.[13] In the second study, the natural history of disease progression was determined from a retrospective chart review on a worldwide cohort of 168 patients with EOPD. The median age at symptom onset was 4 months, median age of first ventilator support was 5.9 months, and median age of death was 8.7 months.[7] Despite intervention, mortality has remained largely unchanged.[7,9,13]

In EOPD, laboratory examination usually reveals cardiomegaly on thoracic radiography; electrocardiogram changes, with a high-voltage QRS complex and short PR interval;[14,15] elevated serum creatine kinase (CK), CK MB isoenzyme (CK-MB), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels; and increases in the level of enzyme of muscle origin, which is more evident with progression of the disorder.[8,16]

In our series of 7 patients with EOPD, the first symptoms were recognized from birth to age 4 months. All 7 patients presented with hypotonia and cardiomegaly, and 4 of the 7 presented with hepatomegaly.

The following syndromes share clinical signs and symptoms with EOPD: spinal muscular atrophy I (MIM 253300), Danon disease (MIM 300257), endocardial fibroelastosis (MIM 305257), carnitine deficiency (MIM 212140), and glycogen storage disease type III (MIM 232400) and IV (MIM 232500).[5,8,17]

LOPD

Symptoms of LOPD may manifest any time after the first year of life up to the sixth decade of life.[4] Progression is slower than in infants but is still relentlessly progressive. By assumption, LOPD does not present with cardiomyopathy; it is characterized by predominantly proximal progressive muscular weakness, with greater impairment of the lower limbs.[8] Usually, paraspinal muscles and lower limb proximal muscles are the first affected, leading to motor impairment and difficulty performing daily activities, and possibly scoliosis, kyphosis, or lordosis. Impairment of the diaphragm and auxiliary respiratory muscles causes chronic respiratory failure along with fatigue, carbon dioxide retention, respiratory insufficiency, and, in many cases, sleep apnea. Repeated aspiration pneumonia is common. Other findings include macroglossia, palpebral ptosis, cerebral aneurism, hyporeflexia, and osteopenia.[18-21]

Muscular weakness is the most prominent symptom, detectable in around 80% of cases and occuring in 95% of cases at some stage of the disease.[19] Respiratory problems resulting from compromised respiratory muscles appear as the first symptom in approximately 11% of patients, occurring at some stage of the disease in 44% of cases.[19,22-24] In our series of 18 confirmed cases of LOPD (9 males and 9 females), the first signs of muscular disorder appeared between age 1 and 42 years (mean, 15.4 years; median, 11 years), and age at diagnosis ranged from 2.5 to 48 years (mean, 25.3 years; median, 23.5 years). Occasionally, dysphagia for solids may result from weakness in the pharyngeal muscles involved in the swallowing reflex. A significant adverse impact on activities of daily living is a common finding.[22]

Laboratory findings include increased CK, AST, and ALT values[16] and spirometric parameters indicating altered respiratory assessment capacity, including forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) in erect and supine positions,[7] with a normal electrocardiogram. In our series, 10 of 18 patients with LOPD required some sort of respiratory support during the course of the disease. Muscle biopsy reveals greatly increased deposition of glycogen within muscle vacuoles, with destruction of myofibrils.[2]

The following syndromes share clinical signs and symptoms with LOPD: limb girdle muscular dystrophy (MIM 253600), Becker/Duchenne muscular dystrophy (MIM 300376/310200), polymyositis, rheumatoid arthritis, and glycogen storage disease type III (MIM 231400), IV (MIM 232500), and V MIM 232600). Further details regarding the differential diagnosis of neuromuscular disease are available at www.musclegenetable.org.[25]

Diagnosis

Patients with a clinical history compatible with PD must be investigated to confirm the diagnosis. Asymptomatic family members of a known patient also should be considered for assessment.[16,25] Hypotonia and cardiomegaly on radiography or cardiomyopathy on echocardiogram are important signs in the clinical examination of infants that includes PD among the diagnostic possibilities.[4,7]

In EOPD, the diagnosis should be made based on measurement of GAA enzymatic activity in a blood sample using filter

paper.[26] Subsequent confirmation should always be done through enzyme activity assays in fibroblast cultures or lymphocyte assays and/or genotyping through DNA analysis.[27-30] It should be noted that the sensitivity and specificity of filter paper testing depend on the method used. Studies comparing acarbose and maltase inhibition have been reported,[31-34] and use of the acarbose method to inhibit the activity of the enzyme maltase-glucoamylase has been recommended recently.[35] Increased urinary excretion of oligossacharides in urine chromatography also may corroborate the diagnosis.[36] In our series of 7 patients with EOPD, all had dried blood spot enzyme assays compatible with the diagnosis of PD; other tests, including leukocyte GAA assay (2 of 7), muscle biopsy (4 of 7), genotyping (7 of 7), and oligossacharide urinary chromatography (4 of 7) confirmed the diagnosis. The GAA assay using skin fibroblasts was once the gold standard, but now the addition of acarbose to assays prevents false-negative results. The reliable, less invasive, more convenient, and faster GAA assay using blood samples can now be considered the method of choice for diagnosing PD.[35]

The assessment of cross-reactive immunologic material (CRIM) status, which detects the presence or absence of native GAA protein on Western blot assay using cultured fibroblasts, is a sensitive and specific test that may be of great value in establishing the prognosis and response to enzyme replacement therapy (ERT). In our series of EOPD patients, 5 of 6 analyzed cases were CRIM-negative. This observation correlates well with the presence of approximately 2560 C > T null mutations in homozygosis or in association with other deleterious mutations in the majority of Brazilian EOPD cases studied to date.[27] Other issues regarding the method and handling of samples are important as well, such as the need to collect frozen muscle biopsy specimens for histochemical analysis, DNA for genotyping, and RNA for gene expression analysis.[37-39]

In older patients, analysis of dry blood spots using filter paper can be a reliable screening test. Abnormal or suspected results should always be confirmed by further testing, including measuring enzymatic activity in lymphocyte or fibroblast assays and/or genotyping by DNA analysis. Muscle biopsy findings also may suggest PD.[27-30,37-39] Increased plasma and urine concentrations of glucose tetrasaccharide, which may serve as a biomarker for diagnostic purposes, have been found; this test is not currently in widespread use, however.

In our series of 18 LOPD patients, all had dried blood spot enzyme assay results compatible with PD. Seventeen patients had vacuolar myopathy with glycogen storage on muscle biopsy, and genotypes comprehending a series of homozygous missense mutations or compound heterozygotes with a combination of missense and intronic mutations or missense and stop codons mutations were identified.[27]

Management

Because PD is a multisystem disorder, it is best managed by a multidisciplinary team led by an experienced physician. Optimally, the team should include a metabolic disease specialist in addition to the specialist dictated by the patient's signs and symptoms, possibly a cardiologist, pulmonologist, neurologist/neuromuscular specialist, orthopedist, physical therapist, speech therapist, geneticist, and/or metabolic dietitian, among others.

Clinical Approach

Cardiology. Cardiomyopathy in patients with PD should be treated cautiously, preferably by a pediatric cardiologist with experience with this disorder. Care must be adjusted to disease stage; inappropriate use of the standard drugs used to treat cardiomyopathy may worsen an already impaired heart. In the earlier phases of the disease, hyperthrophy is predominant with or without left ventricular outflow tract obstruction and normal or even hyperdynamic left ventricular ejection fraction. In the presence of left ventricular outflow tract obstruction, beta-blockers can be used judiciously due to the risk of sudden death.[9] Diuretics also can be used judiciously in patients with pulmonary congestion. The use of digoxin, beta-adrenergic agonists, or afterload-reducing agents, such as angiotensin-converting enzyme inhibitors and diuretics, may exacerbate the left ventricular outflow tract obstruction. But these agents generally are used in the later phases of the disease in the presence of ventricular dysfunction (dilated cardiomyopathy).[3] Some patients present with ventricular dysfunction in the earlier phases of the disease and need to start with these medications. Arrhythmia also may occur, due to the insulator effect of glycogen in conduction tissue[40] and to underlying subendocardial ischemia from inadequate coronary perfusion of a massively hypertrophied ventricle. Therefore, special care must be taken in patients with PD to avoid hypotension if volume depletion occurs or anesthesia is required.[41]

Pulmonology. Approximately 30% of patients with PD require ventilatory support, irrespective of age of symptom onset. Orotracheal intubation must be avoided whenever possible in view of the difficulties in weaning from invasive ventilation and resulting complications, such as fistulas. However, when indicated, an aggressive approach is recommended, especially in infants, given the extremely high vulnerability of these patients. Ideally, bilevel positive-pressure airway ventilation support should be used instead of continuous positive airway pressure, using various inspiratory and expiratory pressure levels. Adults tend to respond well to noninvasive ventilation (NIV).[42] Children present greater adaptive difficulties, although NIV can be used in the event of progressive respiratory insufficiency. Despite NIV, patients may have symptoms of sleep apnea. Bilateral positive pressure airway ventilation should be adjusted (with mandatory frequency during sleep) according to the patient's needs. Muscular weakness can lead to generation of insufficient stimulus to trigger the next cycle of the ventilator. Thus, sleep apnea can be avoided with less thoracic muscular effort and improved sensitization to CO_2 and O_2. It is important that atelectasis be ruled out as the main cause in any respiratory decline in infants.[23,24]

Musculoskeletal. Musculoskeletal involvement in PD is characterized by progressive weakness that leads to decreased motor function, altered postural tendencies and positioning, and the use of compensatory patterns of movement. Secondary musculoskeletal manifestations, such as contractures, deformities, and osteoporosis, can occur and further impair function. Rehabilitation management of PD should be comprehensive and preventive, based on an understanding of the pathokinesiology of disease progression and on individual assessment. It should optimize and preserve motor and physiological function, prevent or minimize secondary complications, and promote and maintain the maximum level of function.[9]

Speech, Swallowing, and Nutritional Assessment. Muscular weakness may lead to difficulty in phonation and in the completion of safe swallowing. Poor swallowing, muscle wasting, increased effort of breathing, and impaired mobility should be considered as factors in undernourishment. Malnutrition may exacerbate the muscle weakness. Several studies have investigated the possible benefits of a high-protein diet in patients with PD. In general, a high-protein diet is recommended and should be administered under the supervision of a metabolic dietician.[43,44] The risk of aspiration should be assessed by a trained speech therapist and also by videofluoroscopy when necessary.

Anesthetic Risk. Patients with EOPD are at high risk for clinical complications from anesthetics due to significant cardiovascular compromise.[41] Surgical procedures should be avoided whenever possible. If anesthesia is necessary, the preferred drug is ketamine, which does not significantly affect pre- and post-cardiac load, thereby avoiding the risk of myocardial ischemia. Propofol, particularly at high doses, and suxamethonium should be avoided. Sedation and local anesthesia (even for gastrostomy, if possible) should be used whenever possible.

ERT. Among the available approaches to treat PD, ERT based on rhGAA has become a major cornerstone in the improved care of these patients.[45-49] Several open-label clinical trials involving patients with EOPD have shown that ERT significantly prolongs survival,[45,50-56] decreases cardiomegaly, and improves cardiac and skeletal muscle function. In the vast majority of cases, cardiac response appears to be good, irrespective of the stage of the disease at the start of ERT. Skeletal muscle response has been more variable than cardiac muscle response. The best skeletal muscle response has been noted in patients treated early, before severe skeletal muscle damage has occurred. There are several EOPD patients on ERT who are walking, a milestone that probably would not have been achieved without ERT. Thus, with the advent of ERT, the natural history of this once-lethal disease has changed, and additional physical and mental disabilities may be uncovered. Some patients have not a good outcome despite early treatment, however. Such factors as muscle fiber type, stage of disease at the start of therapy, genotype, and

immune response to rhGAA may play a role in determining outcome and merit further investigation. Work on a second-generation recombinant enzyme for PD for more efficient targeting to muscles is in preclinical stages.[9]

Gene therapy, small molecules, and chaperones. Progress in the development of gene therapy continues. Studies in Pompe mice have demonstrated that various gene delivery vector systems have potential and demonstrate that expression of the GAA gene within muscle cells decreases the glycogen storage abnormality in the mice. The use of small molecules to treat lysosomal storage disorders, either as a single agent or in combination with other therapies, is emerging as a therapeutic tool. Pharmacologic chaperones that bind to the affected proteins and restore their shape, proper trafficking, and biological activity also may become available for those who can make the protein, most likely those with LOPD.[9]

Following confirmation of the diagnosis of PD, a series of procedures are recommended to establish measurements for both prognosis and therapeutic response. The first step in this process should be teaching parents of children with EOPD and parents and teenagers/adults with LOPD about PD's natural history, genetic basis, and pathophysiology, to properly discuss treatment options and realistic expectations if ERT is to be started.

Pretreatment Assessment

This begins with filling out the anamnesis form available at www.pomperegistry.com. The objective is to create a patient database file based on signs and symptoms before ERT. Such approach ensures a combined series of functional scales and evaluations for different ages, such as the Peabody Developmental Motor Scale (PDMS-2) and the Pediatric Evaluation Scale for PD (PEDI-POMPE).[4,22]

A family history is obtained to ascertain ancestry and consanguinity. The classification by skin color on the PD registry (www.pompe.com) especially for the Brazilian population is open to erroneous interpretations. The classification used by the Latin-American Collaborative Study of Congenital Malformations is much more accurate in this regard, taking into account the panethnic characteristics of the Brazilian population based on 7 different ethnic groups: Latin-European (Portuguese, Italian, Spanish, French, Romenian), non-Latin-European (Caucasian), Jewish (Ashkenazi or Sephardic), Native (Amerindian), Afro-American, Arabic (Turkish, Lebanese, and Syrian), and Oriental (including India).[57] Family history should be reviewed to allow genetic counseling and to identify other cases through the index case.

The following complementary tests are required for patients with EOPD:

- Laboratory tests: CK, CK-MB, AST, and ALT (they remain high throughout follow-up), electrolytes (cardiac dysfunction risk), γ-glutamyl transpeptidase, lactate dehydrogenase, urea, creatinine, hemosediment rate, blood counts, total protein and fractions (albumin [nutritional assessment]) and glycemia. In view of the

frequent respiratory complications, arterial gasometry is highly recommended.

- Polysomnography, when possible. Assessment of hypercapnea peaks during sleep must be assessed, including sleep apnea. At a minimum, heart rate, overnight oxygen saturation, and capnography should be assessed.
- Electrocardiography, to assess for the presence of high-voltage QRS and duration of PR interval according to age, together with T-wave alterations.
- Echocardiography is essential to follow-up therapeutic response. It is important to perform a baseline echocardiogram as close as possible to the initiation of ERT and to assess septum size, end-diastolic volume, and ejection fraction. Ventricular mass and ventricular mass index should be calculated using Devereaux's formula.[15]
- Radiography of the thorax to determine the cardiothoracic index at baseline and in the event of any clinical deterioration.
- Motor assessment to quantify hypotonia and muscular strength. The PEDI-POMPE scale is useful but applies only to patients over age 2 years.
- Swallowing evaluation. Videofluoroscopy is the most widely indicated test for infants under age 4 months.
- Nutritional assessment and monitoring: weight, height, skin triceps fold.
- Physiotherapeutic assessment and monitoring.
- Neurologic assessment.
- Immunologic assessment. Adverse reactions to ERT must be correlated with the immunologic status investigation in each patient, including the CRIM test and IgG- and IgE-mediated reactions, with complement and tryptase investigations. Baseline serum samples can be stored frozen should immunologic investigation be necessary during treatment.
- CRIM test to assess residual enzymatic activity in fibroblast cultures. Collection should be done with a skin punch using local anesthesia. Cultures should be set up for fibroblast culture or done simultaneously with muscle biopsy (with local anesthesia). Biopsy specimens should be snap-frozen to allow proper histochemical and protein studies. Ideally biopsy and the CRIM test should be performed before the start of treatment.

The following complementary tests are required for patients with LOPD. Note that the heterogeneity in the phenotype poses some challenges for standard assessment. Some patients with LOPD are incapable of completing all of the functional tests due to the severity of their condition. Physicians should choose the best of the following tests to document the patient's severity and pattern of motor, respiratory, and functional impairment:

- Laboratory tests: phosphocreatine kinase, CK-MB, aldolase, lactate dehydrogenase, γ-glutamyl transpeptidase, urea, creatinine, electrolytes, arterial blood gas analysis, and hemogram (polycythemia).

- Polysomnography for evidence of hypercapnia or sleep-disordered breathing.
- Pulmonary assessment tests. Some 60% of patients present with an FVC of < 80% and 30% to 40% with an FVC of < 60% of expected values. Testing patients in both the sitting and supine positions is mandatory. The following should be noted: percent decrease of FEV_1 in the supine position, percent decrease of FVC in the supine position, and each parameter in the erect position, expressed as % predicted, along with maximum expiratory pressure, maximum inspiratory pressure, peak cough flow, and arterial or capillary blood gas estimation (pCO_2, pO_2, and pH), specifying whether self-ventilating and whether awake or asleep.
- Motor assessment. Assessment of specific functional activities includes standing posture and alignment (if able to stand), observing for lordosis or scoliosis; paraspinal and other muscle wasting; deep tendon reflexes; contractures; range of joint movement; and ability to walk, climb stairs, stand from a chair, stand from lying on the floor (Gower maneuver), reach for an object, and lift hands to the top of the head, ideally also on video. The PEDI-POMPE scale is extremely useful in older patients with PD because it allows assessment of not only motor function, but also self-care on 2 scales of 0-100. Manual muscle testing (MRC 0-5/5 scale) should be applied to document all main muscle groups: left and right proximal and distal, flexors, extensors, abductors, and adductors. The assessment of range of active movement at each major joint may reveal functional consequences of muscle weakness and may be an early indicator of treatment effect. These tests should be applied systematically to provide quantitative parameters, very important for assessing the therapeutic response.
- Bone densitometry and radiography of the thorax and spinal column, to identify osteopenia and bone deformities.
- Physiotherapy assessment, using an analog visual scale for painful symptoms.
- Echocardiography and electrocardiography. Generally, cardiac alterations are secondary to pulmonary alterations.
- Nutritional assessment.
- Audiometry.
- Quality-of-life questionnaire: SF 36, available at www.pompe.com or www.sf-36.org/.
- Electroneuromyography: myotonic discharges in paravertebral musculature.
- Magnetic resonance spectroscopy of muscle with phosphate and/or lactate marker (single-photon emission computed tomography) or magnetic resonance imaging, using T2-weighted images of pelvic, paravertebral, and scapular muscles to assess for edema and infiltration. This test is largely for academic purposes.

Treatment With ERT

A child or adult patient with a confirmed diagnosis of PD associated with muscle weakness and/or respiratory failure, leading to an impaired quality of life, is a candidate for treatment. A definitive diagnosis, enzymatic or genetic, of acid-maltase deficiency is a requirement but should not alone be an indication to initiate treatment. The physician and family should be aware of the risk of possible complications and the realistic expected benefits, and should be committed and able to follow the recommended protocol for monitoring the response to treatment. The family and physician will have discussed the circumstances under which this treatment is to be started and may be withdrawn. Better outcomes are associated with early diagnosis and therapeutic intervention. However, given the complexity of the disease and the infusion-associated adverse events potentially associated with ERT, particularly in CRIM-negative infants, as demonstrated in all Brazilian-treated patients, it is important to check for the available health care unit infrastructure necessary to safely carry out the infusions. Infants with PD generally are severely ill and more likely to suddenly present with complications. A level-3 hospital with a pediatric intensive care unit is mandatory. Discussion with families regarding the efficacy of ERT and possible side effects is also paramount. Difficulties in predicting response to treatment should be addressed, because prognostic factors that may influence the response to treatment are currently unknown. The multiprofessional team also should be made aware of these difficulties. It is important to determine the baseline measurement, to consider any improvement in or prevention of progression of disease activity indicated by stabilization in clinical condition as an important endpoint to achieve. Furthermore, individualized therapeutic goals should be set based on a panel of monitoring tests that best captures the patient's state of health.

Medical staff training, along with specific guidance for physicians, nurses, and the pharmacy, is recommended before the first therapeutic infusion. Adverse effects must be recorded and forwarded to the pharmaceutical company for pharmacovigilance (Genzyme Serious Adverse Experience/Infusion-Associated Reaction Report, Medical Affairs Pharmacovigilance 675 West Kendall Street Cambridge MA, 02142).

After parental consent, patients diagnosed with EOPD, confirmed by paper filter testing, should be eligible to start treatment without delay. The recommended dose of rhGAA is 20 mg/kg every 2 weeks. The medication should be reconstituted in strict adherence with the manufacturer's instructions. An infusion pump should be set up using a pre-filter (0.2 μ), with a gradually increasing infusion rate (starting at 1 mg/kg/hour and increasing by 2 mg/kg/hour up to a maximum rate of 7 mg/kg/hour). Should the patient exhibit any type of reaction, the infusion rate should be reduced until the patient's condition stabilizes. Discontinuation of infusion is recommended in patients with evidence of fever, infection, or hemodynamic instability. In such cases, infusion should be postponed until these factors have been controlled, at which point the infusion routine should be reestablished as soon as possible. The recommended treatment for LOPD is rhGAA at a dose of 20 mg/kg every 2 weeks.[46,48]

The most frequent adverse reactions are infusion-associated reactions, typically tachycardia, sweating, and flushing due to the protein infusion. These reactions tend to be of mild to moderate intensity and generally respond to slowing the infusion rate or stopping and restarting the infusion once the symptoms have resolved. Children also may experience what adults have described as a "sensation of imminent death," commonly manifested clinically by rapid oxygen desaturation, sudden awakening from sleep, perioral cyanosis, sudoresis, malaise, irritability, and acute crying. Although no controlled studies are available, our clinical experience with nebulization with a β2-agonist has shown that most of these symptoms improve or disappear with this therapy. It also is important to reduce the infusion rate of ERT during such events. The use of premedication is not indicated until the initial occurrence of adverse reactions; the choice must be made on a case-by-case basis. Most adverse reactions occur between the 5th and 15th infusions, but there is no general rule; hence the need for supervision every 30 minutes during the infusion by the nursing staff. Physical monitoring is recommended, with special attention to the cardiorespiratory systems, assessing breath sounds, respiratory rate, heart rate, and blood pressure both before and during infusion.

True IgE-mediated anaphylactic reactions, with cutaneous hypersensitivity, urticaria, respiratory symptoms, especially bronchospasm and/or oxygen desaturation, may occur. Skin testing for rhGAA allergy is recommended in the event of moderate to severe infusion-associated reaction or acute anaphylactoid reaction suggestive of mediation by IgE (ie, persistence of such symptoms such as bronchospasm, hypotension, and/or urticariform reactions).

Older patients with PD, who generally have greater residual enzyme activity and lower antibody levels, tend to experience much fewer, and milder, adverse effects. Nevertheless, if an infusion-associated reaction occurs, regardless of pretreatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of antihistamines and/or antipyretics is indicated to ameliorate the symptoms. If the reaction is thought to be due to anaphylaxis, then IgE antibody, tryptase, and complement levels should be assessed through the manufacturer's pharmacovigilance program. For the next infusion, premedication should not be used if the reaction is thought to be truly due to anaphylaxis, because it could mask potentially severe symptoms. Once serious adverse events have been controlled, resumption of infusion is recommended. The only event precluding infusion is anaphylactic reaction.[46-48]

In our series of 7 EOPD patients, all 7 patients were enrolled in ERT with rhGAA (age range, 2 to 11 months; mean age, 7 months). The 5 CRIM-negative children experienced moderate to severe infusion reactions, including bronchospasm, severe skin rash, and hypotension. A recent report suggests a strong correlation between adverse effects during ERT and a lack of residual enzymatic activity in CRIM-negative patients.[12] This may correspond to the immunologic

response against rhGAA in patients with an absence of constitutional GAA immunologic exposure. In our series, such CRIM-negative patients carried genotypes characterized by homozygous nonsense mutations, resulting in premature stop-codons and lack of residual GAA enzymatic activity.[27]

Eleven of our 18 LOPD patients were on ERT. Therapy started between age 4 and 55 years (mean, 23 years). Although most patients received treatment for only several months, all patients but one reported a positive clinical improvement in the ability to perform daily activities (eg, pouring boiling water from a kettle without assistance, being able to speak loudly enough to be heard from the next room, improving sexual performance, and other anedoctal reports of various aspects of daily life). Importantly, the number of hours without ventilatory support increased, with some needing it only for sleeping. Objective measurements of improved respiratory function and muscle strength are in progress.

Treatment Follow-Up
In infants, follow-up should include the following:

- Motor and respiratory physiotherapy[42]
- Speech therapy: swallowing exercises, even in those without this disturbance
- Nutritional assessment (highly recommended)
- Echocardiography every 3 months. Holter monitoring to detect intermittent arrhythmias, particularly in patients with concentric ventricular hypertrophy, is also recommended.[11,14]
- Monthly clinical assessment conducted outside admission times for ERT, preferably by a physician not directly involved in the infusion routine, aimed at a generalized systematic assessment
- Assessment of motor function based on development protocols for the pediatric age group
- Blood gas analysis every 3 months (highly recommended for detecting chronic hypercapnea)
- Polysomnography, to monitor disease progression and evaluate treatment efficacy in terms of chronic hypercapnea during sleep
- Tracking of osteopenia using spine radiography (L1 to L5) corroborated by bone densitometry
- Muscle magnetic resonance imaging, if available, to detect muscular fibrosis, as well as body mass calculation.
- Audiometry. Given the restrictions imposed on general anesthetic in cases of EOPD, audiometry or otoacoustic tests may be used screen for hearing deficit.
- IgG antibody testing every 3 months (per sponsor guidelines)

For older children and adults, clinical reassessment should be carried out independently every 6 months, and a physiotherapist and/or occupational therapist should be involved in the assessment. Functional motor assessment should include the ability to move around inside and outside the home, ability to transfer from a bed to a chair or from a bed to the standing position, functional aids required to achieve

mobility, ability to perform self-care, and quantitative tests measuring 6-minute walking and climbing stairs on a standardized form. Pulmonary function tests and sleep tests should be performed every year and compared with baseline values. Annual reassessment entails filling out the SF-36 quality-of-life questionnaire (www.sf-36.org/). Muscle magnetic resonance imaging or another quantitative measurement of the muscle involvement is recommended. Motor and respiratory rehabilitation programs, including orthostatic and supine assessment, should be maintained and constantly managed.

A panel of monitoring tests based on the patient's capacity to perform the tests should be determined as a protocol for the treatment follow-up. The therapeutic goals should be set according to the patient's documented functional state, and the consequences of failing to meet these goals should be explained. Stabilization of the condition is considered a therapeutic success. Spirometric assessment of respiratory muscle strength, manual muscle testing, quantitative functional muscle testing, and assessment of activities of daily living should be included in the standardized protocol of follow-up assessment, which will be carried out every 6 months for clinical assessment and every year for complementary examinations. The physician and patient must agree to follow the determined protocol of assessment.

Prognosis and Therapeutic Response
There are no known accurate prognostic factors regarding the response to ERT in patients with PD, in either the EOPD or LOPD form. Preliminary studies suggest that a constitutional absence of native GAA protein on a Western blot assay, described as CRIM-negative, can serve as a predictor of worse treatment prognosis.[12,58] Other prognostic factors should be considered as well, including genotypes carrying mutations that are expected to introduce stop codons and/or null mutations, leading to a premature halt of protein production and CRIM-negative status; muscle biopsy specimens demonstrating extensive impairment of striated muscle with extensive vacuolated fibers; late introduction of ERT; and the presence of comorbidities, such as gastrostomy and tracheostomy. Patients should be evaluated on a case-by-case basis, however. Clinical studies of ERT in infants with PD have focused on ventilator-free survival time as the main treatment outcome.[12] Secondary outcomes have included greater overall survival period, changes in left ventricular mass,[11,14] improvements in weight gain and growth, and improved motor assessment and function indices.[25]

In our series of infants with EOPD receiving ERT, the following factors were associated with worse therapeutic response: initiation of ERT after age 6 months, CRIM-negative status, severe swallowing disturbance, cardiocirculatory shock, and evidence of solid vacuolization on muscle biopsy.

Discontinuation of Treatment
The following variables can serve as a basis for consideration of whether or not to withdraw ERT in EOPD: CRIM-negative status, mechanical ventilation, motor and quality-of-life function (ie, ability to perform activities of daily living,

cognition, fine and gross motor development, and language development), and associated comorbidities. Patients who are too sick at the start of treatment, including those already receiving invasive ventilation for respiratory failure or who have another life-threatening disease, are expected to respond poorly to ERT. All of these aspects should be exhaustively discussed before ERT is commenced.

Negative CRIM status, permanent mechanical ventilation, absence of motor and functional gains, or clinical deterioration due to the presence of comorbidities may point to the need to revise treatment goals. Morphological criteria in muscle, related to irreversible tissue degeneration and increased glycogen deposits despite ERT treatment, also may contribute to the decision of whether or not to suspend treatment. Monitoring functional improvements through clinical assessment and application of the PEDI-POMPE,[4,22] serial echocardiography, and time without mechanical ventilation appear to be the best measures and outcomes currently available to facilitate prognostic assessment.

The development of severe anaphylactic reaction (anaphylactic shock) cals for immediate suspension of ERT. This is perhaps the only point on which there is true consensus. Desensitization has been successfully carried out in some patients, however. A discussion of the case with the patient's family is mandatory. Discontinuation of therapy should be considered in patients in whom criteria for a worse prognosis were present at the start of treatment, patients receiving continuous invasive mechanical ventilation, and patients with an absence of spontaneous motor activity, as well as in cases where it is the family's wish. In this respect, the patient's family of should be kept informed and encouraged to actively participate in the decision related to the initiation or withdrawal of ERT.

It should be kept in mind that because PD is a rare genetic disease involved with a novel treatment proposal, it is important to have the maximum amount of information pertaining to the patient and his or her response to treatment.

Discontinuation of ERT should be considered in patients with LOPD when (1) intolerable and unavoidable adverse effects occur; (2) the patient demonstrates a lack of response to ERT after a minimum period of observation and treatment, as assessed through basal meaures established from the beginning of ERT; (3) the patient wishes to stop ERT; or (4) the patient exhibits insufficient compliance with treatment, where clinical follow-up assessment is not possible.

Conclusion

Despite recent medical advances in the management of PD that have had a significant impact on the disease's natural history, PD continues to be disabling and lethal. The rarity of PD has hindered the necessary systematic clinical studies and establishment of minimal standard clinical care. Brazil is a continental country with a very heterogeneous health care system. Continuous medical education is needed to foster constant improvement in both technology and in health care provision, especially in diagnosing and treating this rare disorder. In view of the multisystemic and com-

plex pathophysiology of PD, standardization of laboratory techniques and liaison among different medical teams should be optimized. Considering the impact of ERT on the health of individuals with PD,[12] discussions regarding treatment strategies for PD should be included in the Brazilian public health arena.[59] Under such circumstances, this consensus can offer the minimal health care guidelines to standardize the clinical management of Brazilian patients with PD.

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