



# Respiratory manifestations in late-onset Pompe disease: a case series conducted in Brazil

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## INTRODUCTION

Pompe disease (PD), also known as glycogen storage disease type II, is an autosomal recessive hereditary disease caused by mutations in the gene encoding acid alpha-glucosidase, an enzyme that is responsible for the degradation of glycogen, especially at the muscle level.

Data on the incidence of PD are inaccurate, because of the rarity, underdiagnosis, and ethnic distribution of the disease. Data from the United States estimate that its overall incidence is approximately 1:40,000.<sup>(1)</sup> More recent studies that have been conducted in Taiwan and Austria and are based on neonatal screening programs have found higher incidences of approximately 1:28,000.<sup>(2,3)</sup> In

## ABSTRACT

**Objective:** To describe respiratory function in a series of patients with late-onset Pompe disease after the definitive diagnosis and before enzyme replacement therapy. **Methods:** This was a cross-sectional study involving patients with a definitive molecular diagnosis of late-onset Pompe disease. The data analyzed included age at symptom onset; age at definitive diagnosis; type of initial symptoms; time from symptom onset to diagnosis; FVC in the sitting and supine positions; six-minute walk distance; and locomotor ability. Analyses were carried out using frequencies, medians, minimum values, and maximum values. **Results:** Six patients were included in the study. The median age at symptom onset was 15 years (range, 13-50 years), and the median age at diagnosis was 39.5 years (range, 10-64 years). The median time from symptom onset to diagnosis was 8 years (range, 0-45 years). In all cases, the initial manifestation of the disease had been motor weakness. The median FVC in percentage of the predicted value (FVC%) in the sitting and supine positions was 71.0% (range, 22.9-104.6%) and 58.0% (range, 10.9-106.9%), respectively. The median  $\Delta$ FVC% was 24.5% (range, -4.59 to 52.40%). The median six-minute walk distance was 391.7 m (range, 97-702 m). **Conclusions:** In this case series, the time from symptom onset to diagnosis was long. Although respiratory signs or symptoms were not the initial manifestations of the disease, 66.7% of the patients showed reduced FVC% in the sitting and supine positions at diagnosis.

**Keywords:** Glycogen storage disease type II; Respiratory function tests; Respiratory muscles/pathology.

Latin America, only 88 patients had been reported to have the disease by 2012.<sup>(4)</sup> Data from Brazil are unavailable.

PD is characterized by lysosomal accumulation of glycogen, especially in skeletal and cardiac striated muscles, beginning when acid alpha-glucosidase activity falls below the critical level of 30%. It is classified as classic infantile PD, with symptom onset occurring before the first year of life, accounting for approximately 28% of all cases; and as late-onset PD, when symptoms appear after that period, including children, youths, and adults. Disease progression in late-onset PD is slower than that in infantile PD, but it is quite variable. Clinical manifestations and disease severity vary according to age at symptom onset, rate of progression, and extent of organ involvement.<sup>(5-7)</sup>

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Until recently, treatment of PD was considered to be only palliative. In 2006, the commercial use of enzyme replacement therapy (ERT) with recombinant human alpha-glucosidase (alglucosidase alpha; Myozyme®, Genzyme, Cambridge, MA, USA) was approved in the USA and Europe, and, in 2007, it was also approved in Brazil. The treatment seems to improve respiratory and locomotor functions, as well as survival, in both forms of the disease.<sup>(8-10)</sup>

Muscle weakness is the major symptom in late-onset PD. The paravertebral and proximal lower limb muscles are usually the first to be affected, making it difficult to perform activities of daily living and favoring postural changes.<sup>(5)</sup> The respiratory consequences of muscle weakness result in restrictive lung disease, with a reduction in vital capacity accompanied by a reduction in FEV<sub>1</sub>. Initially, breathing is compromised only during sleep, but later on, hypoventilation will occur during the day as well. There is impairment in the cough mechanism and airway clearance, leading to recurrent respiratory infections. Respiratory dysfunction will occur in approximately 75% of patients.<sup>(11)</sup> Without treatment, FVC is expected to decrease by 1.0% to 4.6% annually.<sup>(5,12,13)</sup> Respiratory failure is the major cause of death.<sup>(14-16)</sup>

The predominance of diaphragmatic weakness over weakness of other respiratory muscles seems to be a characteristic of PD.<sup>(17,18)</sup> Therefore, the use of methods capable of assessing the activity of the diaphragm alone can be useful in describing and monitoring the disease. Measurement of transdiaphragmatic pressure is the gold standard for the diagnosis of diaphragmatic dysfunction; however, other simpler methods, such as measurement of FVC in the supine position and difference between sitting and supine FVC have been described and recommended for the clinical follow-up of PD.<sup>(16,19-21)</sup>

At present, little is known about pulmonary manifestations in patients with PD in Brazil, which contributes to the management difficulty in this population. The objective of the present study was to characterize the profile of patients with PD and to describe respiratory function in a series of such patients followed at a referral center for rare diseases in Brazil, after the definitive diagnosis and before ERT.

## METHODS

This was a cross-sectional study involving data obtained from the medical records of patients with a definitive diagnosis of late-onset PD and followed at the Center for Medical Genetics of the Fernandes Figueira National Institute for Women's, Children's, and Adolescents' Health, *Fundação Oswaldo Cruz* (Fiocruz, Oswaldo Cruz Foundation), located in the city of Rio de Janeiro, Brazil, between 2010 and 2015. Data on clinical history and respiratory function for the period after the diagnosis and prior to the initiation of ERT were analyzed. The exclusion criterion was a lack of data on respiratory function at diagnosis. The study

was approved by the local research ethics committee, as part of the International Pompe Disease Registry.

Patient's characteristics and clinical history included data on gender, type of pathogenic mutation, age at symptom onset, type of initial symptoms (motor or respiratory), age at definitive diagnosis, and time from symptom onset to definitive molecular diagnosis. The major initial motor symptoms that are commonly reported and described for PD and that were sought from the medical records included lower limb proximal muscle weakness and/or upper limb proximal muscle weakness; difficulty running, climbing stairs, or walking; frequent falls; trunk muscle weakness; and scoliosis. Respiratory symptoms included orthopnea, dyspnea after exercise, dyspnea at rest, and sleep-disordered breathing.<sup>(22)</sup> The sample was further characterized on the basis of locomotor function as assessed by the Walton and Gardner-Medwin (WGM) scale<sup>(23)</sup> and the six-minute walk distance (6MWD). The WGM scale characterizes locomotor ability and has a score ranging from 0 to 10, with 0 indicating that the patient performs all activities normally and 10 indicating that the patient is completely bedridden. The 6MWD was recorded in meters and as a percentage of the predicted value, using equations from Iwama et al.<sup>(24)</sup> and Priesnitz et al.,<sup>(25)</sup> for each age group.

The respiratory function variables of interest included FVC, as measured in the sitting and supine positions, and FEV<sub>1</sub>, both of which are expressed as a percentage of the predicted value (FVC% and FEV<sub>1</sub>%); as well as FEV<sub>1</sub>/FVC ratio (in %)<sup>(26)</sup>; difference between sitting and supine FVC ( $\Delta$ FVC%), as calculated using the equation  $[(\text{sitting FVC} - \text{supine FVC})/\text{sitting FVC}] \times 100$ ; use of (invasive or noninvasive) mechanical ventilatory support; and presence of an artificial airway. Volumes were measured with a MasterScope® spirometer (Jaeger, Hoenberg, Germany), in accordance with the criteria established by the American Thoracic Society,<sup>(27)</sup> and FVC values  $\geq 80\%$  of predicted were considered normal for the sitting position.

Data were analyzed using descriptive statistics via IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Nominal variables are presented as frequency, and numerical variables are presented as median and range (minimum to maximum).

## RESULTS

During the study period, we identified seven patients with late-onset PD, all of whom were followed at the institution. Only one patient was excluded because he had no spirometry results for the period in question. The individual results are described in Tables 1 and 2. Of the included patients, four (66.7%) were male. All patients were compound heterozygous for the mutation found. The intronic mutation c-32-13T>G, which is known as potentially mild, was present in 100% of the cases, and the nonsense mutation c.2560C>T, which is known as very severe,<sup>(28)</sup> was present in three (50%) of the cases.

The median age at symptom onset was 15 years (range, 13-50 years), and muscle weakness was found as the initial symptom in all patients, except in patient 2, who was asymptomatic at diagnosis. Frequent falls and difficulty climbing stairs, running, or performing vigorous exercise were reported. The median age at diagnosis was 39.5 years (range, 10-63 years), and diagnosis was made in two adolescents and four adults in accordance with the criteria established by the World Health Organization. The median time from first symptoms to confirmation of the diagnosis of PD was 8 years (range, 0-45 years), ranging from 0 to 2 years for the adolescents and from 4 to 45 years for the adults. All patients were able to walk. The minimum WGM scale score achieved was zero and the maximum WGM scale score achieved was 6, which indicates walking only with assistance. The median 6MWD was 391.7 m (range, 97-702 m and 19-110% of the predicted value for age).

Taking into account FVC in the sitting position, four patients (66.7%) showed respiratory system impairment at diagnosis, with FVC% < 80% of predicted and normal FEV<sub>1</sub>/FVC ratio, characterizing restrictive lung disease, as is expected for neuromuscular diseases. Only one patient already used noninvasive mechanical ventilatory support intermittently, being the one who showed the lowest FVC% in the sitting and supine positions (22.9% and 10.9%, respectively) and the highest ΔFVC% (52.38%). None of the patients used invasive ventilatory support or had been tracheostomized. The median FVC% in the sitting position was 71% (range, 22.9-104.6%), the median FVC% in the supine position was 58% (range, 10.9-106.9%), the median ΔFVC%

was 24.5% (range, -4.59% to 52.4%), the median FEV<sub>1</sub>% was 70.35% (range, 27.0-106.8%), and the median FEV<sub>1</sub>/FVC ratio (in %) was 102.4% (range, 96.3-118.0%). Stratification by age group showed that only two adolescents had spirometry results within the normal range.

## DISCUSSION

The clinical history characteristics of our patients with PD were similar to those found in the literature. The type of initial symptoms was predominantly motor, the median age at diagnosis was 39.5 years, and the delay between symptom onset and diagnosis was 8 years. Data from Byrne et al.,<sup>(16)</sup> obtained through analysis of the PD patient registry administered by the Genzyme Corporation, revealed a predominance of motor symptoms, a median age at diagnosis of 37.1 years, and a delay in diagnosis of 4 years. The delay in diagnosis was slightly greater in the analysis carried out by Kishnani et al.<sup>(22)</sup> The median age at symptom onset was lower in our group of patients (15.0 years vs. 28.8 years).

The rarity of PD, the variability of its clinical presentation, its overlap of signs and symptoms with other neuromuscular diseases, and limited access to the health care system often result in a very long time to diagnosis. The delay in diagnosis seems to be greater in older subjects, which indicates improved knowledge of the disease today.<sup>(16,22)</sup> Taking into account that patients who are younger and less severely affected respond more favorably to administration of ERT,<sup>(13)</sup> the importance of early diagnosis and early treatment initiation is evident.

**Table 1.** General description of the patients in the present case series.<sup>a</sup>

ID	Gender	Birth, year	AGA mutation		Age at symptom onset, years	Type of initial symptoms	Age at molecular diagnosis, years	Delay in diagnosis, years
			Allele 1	Allele 2				
1	M	1992	c.-32-13T>G	c.2560C>T	15	Motor	17	2
2	F	2000	c.-32-13T>G	c.2560C>T	-	Asymptomatic	10	-
3	M	1988	c.-32-13T>G	c.2646+2T>A	13	Motor	25	10
4*	M	1958	c.-32-13T>G	c.1912G>T	50	Motor	54	4
5**	M	1954	c.-32-13T>G	c.1912G>T	13	Motor	58	45
6	F	1951	c.2560C>T	c.-32-13T>G	40	Motor	63	23

ID: identification; F: female; and M: male. \*Patients 1 and 2 and patients 4 and 5 were siblings.

**Table 2.** Functional description of the patients in the present case series.

ID	Sitting FVC, % of predicted	Supine FVC, % of predicted	ΔFVC, %	FEV <sub>1</sub> , % of predicted	FEV <sub>1</sub> /FVC, % of predicted	Ventilatory support	WGM scale score	6MWD	
								m	% of predicted
1	104.6	94.4	9.72	106.8	100.7	No	0	500	77
2	102.2	106.9	-4.59	105.7	104	No	0	495	79
3	58.5	48.4	17.31	65.7	111.6	No	1	702	110
4	60.7	42.2	30.45	58.7	96.3	No	3	376	64
5	22.9	10.9	52.38	27	118	Yes	6	180	39
6	77	45	41.63	75	100	No	6	97	19

ID: identification; ΔFVC: difference between sitting and supine FVC; WGM: Walton and Gardner-Medwin; and 6MWD: six-minute walk distance.

More than 500 mutations have currently been identified, and the expected effects range from very severe to non-pathogenic.<sup>(28)</sup> The mutation most commonly observed in our group of patients is also the one most commonly reported by other authors.<sup>(16,29)</sup> However, the phenotypic behavior is not explained exclusively by the genotype found, especially in late-onset disease. Phenotypic differences are present even in members of the same family, including siblings.<sup>(29)</sup> Patients 1 and 2 and patients 4 and 5, respectively, were siblings with the disease. In both cases, differences were observed in presentation and severity. However, the diagnosis of the younger siblings was facilitated by their family history, enabling a better functional condition at diagnosis. Records show that 32% of patients with late-onset PD had a sibling with a diagnosis of PD<sup>(16)</sup>; therefore, we believe that family screening may be useful in identifying asymptomatic patients and may contribute to a better prognosis.

Monitoring of respiratory function in patients with PD is imperative.<sup>(6,7,20)</sup> In 2013, Ambrosino et al.<sup>(21)</sup> described basic management of respiratory dysfunction in PD, including periodic evaluations every 3-12 months, depending on the rate of disease progression; monitoring of respiratory signs and symptoms; spirometry in the sitting and supine positions; measurement of MIP; measurement of peak cough flow; blood gas analysis; and, in some cases, polysomnography and swallowing studies. Consensus statements and guidelines for the management of PD also have similar recommendations.<sup>(6,7,20,30)</sup>

The pathophysiology of chronic respiratory failure in neuromuscular diseases includes not only respiratory muscle weakness but also changes in chest wall compliance, central respiratory control, and swallowing, which, in turn, are responsible for Ineffective cough, alveolar hypoventilation, chest deformities, sleep apnea, atelectasis, airway hyperreactivity, and recurrent pneumonia.<sup>(31)</sup> Unlike other neuromuscular diseases, in which loss of walking ability precedes ventilatory failure,<sup>(5,17)</sup> in PD, respiratory symptoms may manifest early, being the initial symptom in 8.5% of cases.<sup>(4)</sup> Despite our small sample size, the results for locomotor ability and the 6MWD results, when compared against the spirometry results, seem to corroborate the hypothesis that impairment of the respiratory and locomotor systems is heterogeneous.<sup>(32)</sup> The patient with the greatest 6MWD already showed reduced FVC% in the sitting and supine positions and reduced  $\Delta$ FVC%, whereas the patient with the shortest 6MWD did not have the most severe lung disease.

In our study, none of the patients followed had respiratory symptoms as the first manifestation. However, at diagnosis, we observed signs of respiratory system impairment, as identified by reduced FVC% in the sitting position (FVC < 80% of predicted), in 66.7% of them. Despite the absence of respiratory symptoms as the initial manifestation of the disease and the delay between symptom onset and the first spirometry, we cannot rule out the existence of some

degree of respiratory impairment in the very early stages of PD, but without ignoring that age and duration of symptomatic disease also seem to contribute to a worsening of functional findings. It is possible that mild respiratory symptoms were present but went unnoticed because they overlapped with motor symptoms that were more prominent. Questioning and standardized description of the signs and symptoms found, especially at the onset of the disease, may facilitate knowledge and follow-up of patients.

Measures of respiratory muscle strength such as MIP and MEP may be highly relevant to identifying the onset of respiratory muscle impairment, given that changes in them may precede volume reduction as identified by vital capacity. Unfortunately, in our group of patients, we found no such data in the medical records of one of the patients, and two were unable to perform acceptable and reproducible maneuvers. Therefore, MIP and MEP measures could not be included in the analysis, and this represents a limitation of the study.

Diaphragmatic weakness is a dysfunction that is characteristic of PD,<sup>(17,18)</sup> being considered the major cause of disordered breathing during sleep and respiratory failure.<sup>(33)</sup> Prigent et al.,<sup>(34)</sup> using magnetic stimulation of the phrenic nerve, and Wens et al.,<sup>(18)</sup> using magnetic resonance imaging, confirmed the predominance of diaphragmatic weakness over weakness of thoracic respiratory muscles in PD. The most accurate method for assessing diaphragmatic function is to measure transdiaphragmatic pressure during maximal respiratory effort or during spontaneous breathing or use bilateral magnetic stimulation of the phrenic nerves. These methods have the disadvantage of being invasive and not being well accepted by patients, especially when they need to be repeated several times, resulting in them rarely being indicated in clinical practice.<sup>(35)</sup> A simpler way to assess diaphragmatic weakness is to measure sitting and supine FVC% and calculate their difference, which correlates strongly with variation in cranio-caudal diameter as observed by magnetic resonance imaging.<sup>(18,36)</sup> Normal subjects may show a reduction from sitting to supine FVC% as high as 10%.<sup>(37)</sup> Reductions > 25% characterize diaphragmatic weakness, with a sensitivity of 79% and a specificity of 90%.<sup>(19)</sup> In our sample, 66.7% of the patients showed  $\Delta$ FVC% > 10%, and 50% showed  $\Delta$ FVC% > 25%. This assessment is recommended for the diagnosis and follow-up of patients with PD because it is a potential marker of the severity of the respiratory dysfunction. A > 10% reduction strengthens the diagnosis of PD.<sup>(30)</sup> Other methods have also been described for diaphragmatic assessment, including fluoroscopy, ultrasonography, electromyography, and optoelectronic plethysmography<sup>(38)</sup>; however, they are still infrequently used in clinical practice in PD.

The explanation for the predominance of diaphragmatic involvement in respiratory dysfunction remains unclear. Animal model studies suggest that muscle damage is associated with spinal motoneuron pathology, especially phrenic motoneuron pathology,



and this contributes to a more pronounced deficit in the motor function of the diaphragm.<sup>(17,39,40)</sup>

As respiratory muscle weakness progresses, the use of noninvasive ventilatory support is indicated, helping to control nocturnal hypoventilation and sleep apnea syndrome, as well as acute and chronic respiratory failure.<sup>(14,21)</sup> Only one patient in our case series used this resource. Specific indications regarding when to start using ventilatory support in PD have not been described. The use of recommendations for neuromuscular diseases in general contributes to this process.

Respiratory system involvement was present in 66.7% of our patient sample, and diaphragmatic

dysfunction as characterized by  $\Delta FVC\% > 25\%$  was present in 50% of our series at diagnosis, suggesting that even if it is not the initial manifestation, respiratory system involvement may occur early in a significant number of cases. Further studies are needed for a better understanding of this involvement, especially of diaphragmatic dysfunction. The sign and symptom profile used by Llerena et al.<sup>(7)</sup> and Kishnani et al.,<sup>(22)</sup> the recommendations included in the International Pompe Disease Registry, and the respiratory management proposed by Ambrosino et al.<sup>(21)</sup> may be of great importance in the approach to patients with suspected PD or already diagnosed with PD.

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