

# Evaluation of clinical and functional abnormalities in Pompe disease: Case Report

## *Avaliação das anomalias clínico-funcionais na doença de Pompe: Relato de Caso*

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### ABSTRACT

The patient was a 15 year-old girl who turned out at the Physical Therapy Clinic presenting progressive scoliosis and angle of 50° Cobb by X-Ray. She complained of back pain, headache and weakness of shoulder and pelvic girdle. Physical therapy evaluation came across features of delayed motor development and undernourishment, together with generalized muscle weakness (grade = 4) which was observed by the Kendall test. Lung vital capacity was 40.5%. Clinical Changes: studies of the enzymes with acid alpha-glucosidase assay kits used on filter paper and leukocytes showed low enzyme activity, suggesting a late form of the Pompe disease. The molecular studies proved that the patient had a mutation associated with late-onset Pompe disease. Acid alpha-glucosidase enzyme assay studies performed in skin fibroblasts showed a reduction of the enzymatic activity of the acid alpha-glucosidase, confirming the previous results. On account of the results, Pompe disease induced important changes in clinical and functional, as well as metabolic changes, decreased strength and muscle action potentially, biomechanical changes in the spine and changes in respiratory capacity. Furthermore, this case of Pompe disease illustrates the importance of adequate physical therapy evaluation as it can be the starting point of investigation of serious conditions such as late onset Pompe disease.

**Keywords:** Musculoskeletal Abnormalities. Glycogen Storage Disease. Glycogen Storage Disease Type II. Biomechanics. Scoliosis.

### Introduction

Pompe disease is a rare autosomal recessive myopathy caused by a deficiency of acid alpha-glu-

cosidase enzyme, leading to an intracellular accumulation of glycogen, particularly affecting the myocardium, the skeletal muscle and the liver. The rupture of lysosomes results in cellular dysfunction, abnormal au-

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tophagy and structural disorganization with primarily symptoms related to progressive dysfunction of skeletal and respiratory muscles.<sup>1,2</sup>

The replacement of myofibrils by glycogen occurs in the muscle tissue, resulting in loss of contractile capacity of muscle, hypotonia and in some cases, hard consistency on touch due to the underlying muscle swelling.<sup>2,3</sup>

The incidence of Pompe disease in infants range from approximately 1:138,000 live births, but it is usually fatal within the first year of life. In teenagers, the incidence of Pompe disease has been estimated to be 1:720,000, whereas the incidence in adults in some cases is as high as 1:53,000, which shows a large clinical variability. Regardless, the combined incidence of the Pompe disease has been suggested to be approximately 1:40,000. In any circumstance, the involvement of multiple systems leads to progressive weakness and disability.<sup>4,5</sup>

There are few studies on clinical and functional evaluation of patients who developed Pompe disease. Therefore, the investigation and description of this syndrome may help improving the understanding of the symptoms of the disease and contribute to new therapeutic approaches. Thus, the purpose of this study is to describe the clinical and functional changes of the late-onset Pompe disease.

## Case Report

The study was approved by the human research ethics committee of Universidade de Franca – Unifran (Franca University), under the protocol: Ref: n # 077/2011.

A 15 year-old female patient was sent to the Physical Therapy Clinic at Universidade de Franca (Unifran) due to the presence of progressive scoliosis. At the moment of the evaluation, the patient weighted 35 kilograms, was 1.48 meters tall and her body mass index (BMI) was 15.98 kg/m<sup>2</sup>. The patient's main complaints were back and leg pain and difficulty in performing any physical activity due to fatigue and decreased breathing capacity.

During postural evaluation, the highest involvement was observed in the anterior view: higher right shoulder, bigger Thales right angle, higher right iliac crest, valgus knee and ankle. Regarding posterior view, it was observed bent head and neck to the right, higher right scapula and a right inclination of the spine. In the lateral view, it was observed a protrusion of the head

and shoulders, with steepening of the lumbar pelvic anteversion.

General muscle weakness was observed throughout the muscle strength test. The tests were divided into: upper limb, lower limb and trunk. The lower limb muscles tested were: hip flexors, extensors, abductors and adductors; knee flexors and extensors; ankle dorsiflexors and plantiflexors. The upper limb muscles tested were: shoulder flexors, extensors, adductors and abductors; elbow flexors and extensors; wrist flexors and extensors. All tested muscles were classified as grade four of strength. Trunk muscles which were tested comprised the obliques, the upper and lower rectus abdominis and extensors of the spine and all have been classified as regular, as proposed by Kendall.<sup>6</sup> In the retraction test significant shortening of the hamstrings, iliopsoas and major and minor pectoralis were observed.<sup>6</sup>

The radiographic exam confirmed right convex thoracic scoliosis, with Coob angle of 50° (**Figure 1**).



**Figure 1.** X-ray anterior to posterior. Note scoliosis the convex right angle 50° of Coob.

## Medical clinical evaluation

After physical therapy evaluation, more than just a change of posture (scoliosis) was observed, and the patient was forwarded to Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade of São Paulo, HC-FMRP-USP (Ribeirão Preto Medicine School Hospital, University of São Paulo) to determine genetic causes of this progressive scoliosis. In the clinical evaluation by a Neurogenetics team of the HC-FMRP-USP, a genetic investigation on the late-onset spinal muscular atrophy was requested, as well as investigation on the connective tissues disorders and limb-girdle myopathies. The molecular examination was normal for spinal muscular atrophy, however, the enzyme assays for alpha-glucosidase (acid maltase) on filter paper and leukocytes showed low enzyme activity, which suggested late-onset Pompe disease (LOPD). In the molecular analysis, the presence of mutation c.-32-13T > G in the GAA gene (which encodes the enzyme alpha-glucosidase) was identified. This mutation is already described in the literature and associated with cases of late-onset Pompe disease (LOPD). To confirm the previous findings, we carried out patient's skin biopsy for fibroblast culture and subsequent enzymatic assays to investigate the deficiency of acid alpha-glucosidase. This analysis showed a reduction of the enzymatic activity (30% of normal values), thus confirming the diagnosis of the LOPD.

After biochemical and molecular confirmation of the disease and worsening of the respiratory capacity of the patient, it was decided to begin the treatment with recombinant enzyme in an attempt to stabilize the patient's clinical status before other clinical parameters were affected.

Currently, the patient is under treatment with recombinant enzyme alpha-glucosidase (Myozyme®), which is administered fortnightly. Also, the patient has been regularly monitored by a team of physical therapists at Universidade de Franca - Unifran for muscle and pulmonary rehabilitation and maintenance of functionality.

## Muscle electrical activity evaluation

The muscle activity was captured within the surface of electromyography (sEMG) using bipolar differential electrodes with a preamplifier (Gain x 20) from EMG System do Brasil Ltda.®. The sEMG sig-

nals were filtered using a bandwidth of 20 Hz to 450 Hz and sampled at 1024 Hz. The sEMG electrodes were placed on the skin over the muscle bellies of the biceps brachii, the rectus abdominis and the rectus femoris corresponding to each body segment. After data collection, the average root means square (RMS) values of the surface EMG signals were calculated for all muscles.<sup>7-10</sup> The RMS values obtained were normalized due to the RMS values obtained in the activity of maximum voluntary isometric contraction (MVIC) and multiplied by 100.<sup>11</sup>

The sEMG signal presented lower values for the biceps brachii (mean = 24uV - 52%), the rectus abdominis (mean = 35uV - 45%) and the rectus femoris (mean = 97uV - 47%). The low electrical activity of the muscle resulted in a lower recruitment of motor units<sup>12</sup>, added four points to the level of muscle strength during the test, what suggested a generalized muscle weakness<sup>10</sup>, similar to delayed motor development and undernutrition.

## Respiratory capacity evaluation

The ventilatory lung evaluation was analyzed through test and lung function, using the apparatus microQuark (Cosmed). The value of forced vital capacity (FVC) was 40.5%, forced expiratory volume (FEV1) of 38.4%, index Tiffeneau 94.7%, and peak flow (PF) of 36.3%, which was the best value obtained. The patient complained of fatigue after minor physical effort, headaches, difficulty breathing and sleeping, therefore, non-invasive ventilation was introduced during the night (BiPAP Synchrony).

## Discussion

Pompe disease involves progressive muscle injury, with proximal muscle weakness, extreme clinical variability among patients and between different muscle groups of same patient.<sup>13</sup> Non-invasive sEMG was applied as a resource for capturing the myoelectric signal resulting from the potential action of the muscle fibers, which occurs before its contraction, to evaluate the electrical activity of muscles during movement, the synchronization of muscles activation, the intensity and duration of muscle contraction.<sup>14</sup>

The biceps brachii, the rectus femoris and the rectus abdominis and the right hemibody were evaluated in this study because these muscles are extremely important to maintain good posture and execution of

tasks.<sup>15</sup> All signals captured were considered low, with a slight signal of muscle fatigue. The sEMG signals for the rectus abdominis and the rectus femoris muscles were lower than the biceps brachii. These low values are consistent with the observed muscle weakness which was found in the muscle strength test performed and justifies the patient's difficulty in changing positions: lying to sitting/standing and in the execution of moderate physical activity. Also with regard to the electromyography findings, studies show that typical muscle weakness and hypotonia are more severe in lower limbs than in upper limbs. Subsequently, the involvement of the trunk muscles (postural changes) was noticed although not all the areas were affected in the same way. Some patients have unsteady gait and occasionally walk on tiptoe.<sup>1</sup>

According to the literature, muscle weakness is due to affected muscle or motor neurons of the ventral horn, similar to what happens with the skeletal muscle phenotype in cases of spinal muscle atrophy. In teenagers and adult forms, the skeletal muscle involvement prevails, often similar to what was seen in girdle muscular dystrophies. In addition, histological examination of biopsy shows that the skeletal muscle fibers exhibit empty spaces which correspond with the deposits of vacuolar glycogen dissolved during the process, and complete distortion of the architecture of the fibers, supporting the findings of Schoser et al. in 2007.<sup>16</sup>

Histopathological diagnosis of teenager's Pompe disease (glycogen storage disease type II) can be done through a study of histoenzymology and electron microscopy of muscle biopsies. Frozen sections of the muscle stained with hematoxylin and eosin showed a variation in the diameter of the muscle fibers, the internalization of nucleic and cytoplasmic vacuoles with the technique of PAS and PAS with diastasis digestion seems to retain intracytoplasmic glycogen.<sup>17</sup> Mainly, in this disease, there is no presence of fibrosis when staining by the Masson trichrome method, and intranuclear hyperglycogenose is not observed.<sup>18</sup> The main feature of it is the increase of the acid phosphatase activity, with excessive lysosomal material.<sup>19</sup>

The ultrastructural study revealed a sharp increase in the amount of glycogen, which occupies a large volume of the myofiber. This glycogen may be inside vacuoles limited by membranes or may be free in the cytoplasm. The large accumulation of glycogen

leads to the reduction of contractile myofibrils and in some cases it can reduce the muscle fiber to an enormous amount of glycogen limited by sarcolemma.<sup>20</sup>

Regarding the ventilatory capacity reduction that results in pulmonary restriction can be a consequence of its own muscle weakness and biomechanical alteration of the chest, due to the presence of scoliosis. The percentage of patients with Pompe disease who have some lung dysfunction is high, reaching 75% of adults and 59% of children.<sup>14</sup> According to the "American College of Chest Physicians" (ACCP), the introduction of non-invasive ventilatory support in patients with restrictive lung frames leading to neuromuscular disease should be considered in the presence of symptoms such as fatigue, dyspnea, morning headaches, associated with at least one of the following functional changes: (i) PaCO<sub>2</sub>  $\geq$  45 mmHg; (ii) nocturnal oximetry showing oxygen saturation  $\leq$  88% for five consecutive minutes; (iii) maximal inspiratory pressure  $<$  60 cm H<sub>2</sub>O or FVC  $<$  50% predicted.<sup>14</sup> Following these criteria, the use of non-invasive ventilation (BiPAP) was prescribed for the patient and in some cases, this may progress to the invasive ventilation method.

The presence of scoliosis is relatively common in patients with Pompe disease. In a similar study conducted by van der Beek et al. in 2011<sup>21</sup>, it was observed that the percentage of patients with scoliosis varied according to age, being more common in children (47%) when compared to adults (28%). The scoliosis of the patient studied is considered serious, requiring surgical intervention in order to correct spinal curvature. However, as the patient is reaching the end of the growth phase and is in enzyme replacement treatment, a conservative treatment was considered, using a brace and physical therapy intervention with postural exercises.

This case showed that Pompe disease induced important clinical and functional, as well as metabolic changes, decreased strength and muscle action potential, biomechanical changes in the spine and changes in respiratory capacity. Furthermore, this case illustrates the importance of adequate physical therapy evaluation as it can be the starting point of investigation of serious conditions such as the present case of LOPD, as well as the multidisciplinary approach, gathering the physical therapy team and other health professionals taking care of the patient.

## RESUMO

Paciente do sexo feminino com 15 anos, apresentou-se na Clínica de Fisioterapia, devido à presença de escoliose progressiva com ângulo de Coob de 50° pelo Raio-X. Apresentou queixa de dor na coluna e na cabeça, fraqueza de cintura escapular e pélvica. Na avaliação fisioterapêutica observou-se um quadro semelhante ao atraso do desenvolvimento motor e desnutrição, com fraqueza muscular generalizada (grau = 4) observada pelo teste de Kendall. Na função pulmonar a capacidade vital apresentou com 40,5%. Estudos enzimáticos com dosagem da alfa-glicosidase ácida em papel-filtro e leucócitos evidenciaram baixa atividade enzimática, sugestivo de forma tardia da doença de Pompe. No estudo molecular, comprovou-se que a paciente possuía mutação associada à forma tardia da doença; estudos enzimáticos da alfa-glicosidase ácida em fibroblastos cultivados a partir de biópsia de pele evidenciaram redução da atividade enzimática da alfa-glicosidase ácida, confirmando estudos enzimáticos prévios. Perante os resultados, a doença de Pompe apresentou alterações clínicas e funcionais importantes como alteração do metabolismo, diminuição de força e do potencial de ação da musculatura, alterações biomecânicas na coluna e na capacidade respiratória. Adicionalmente, o caso ilustra a importância da avaliação fisioterapêutica adequada, pois ele pode ser o ponto de partida da investigação de doenças graves como o presente caso.

**Palavras-Chave:** Anormalidades Musculoesqueléticas. Doença de Depósito de Glicogênio. Doença de Depósito de Glicogênio Tipo II. Biomecânica. Escoliose.

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