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PREVENTION & REHABILITATION: Case Report

The effectiveness of a therapist-oriented home rehabilitation program for a patient with acromegaly: A case study

Tatiana Rafaela Lemos Lima [a], Leandro Kasuki [b, c], Monica Roberto Gadelha [b, c], Agnaldo José Lopes [a, d, *]

[a] Rehabilitation Sciences Post-graduate Program, Centro Universitário Augusto Motta (UNISUAM), Rio de Janeiro, Brazil
[b] Neuroendocrinology Research Center/Endocrinology Section, Medical School and Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil
[c] Neuroendocrine Unit, Instituto Estadual do Cérebro Paulo Niemeyer, Secretaria de Estado de Saúde do Rio de Janeiro, Rio de Janeiro, Brazil
[d] Post-graduate Program in Medical Sciences, School of Medical Sciences, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, Brazil

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ABSTRACT

Background: Acromegaly causes numerous functional limitations that negatively impact patients' performance of activities of daily living (ADLs) and contribute to the deterioration of health-related quality of life (HRQoL). Thus, the purpose of the present case study was to evaluate the effect of therapist-oriented home rehabilitation (TOHR) for a patient with acromegaly.
Case description: We report the case of a 53-year-old man who was diagnosed with primary acromegaly 17 years ago. He complained of difficulties performing tasks that involved his hands, pain in the lower limbs, and fatigue when he climbed a few flights of stairs. Although he performed ADLs independently, he reported some difficulties or discomfort when performing them.
Intervention and outcome: The patient underwent a booklet-guided physical exercise program that lasted two months (three times per week, 60 minutes per session). The activities included overall stretching, muscle strengthening, and endurance exercises, along with aerobic conditioning through functional circuit training. After two months of exercise, he reported improved HRQoL as assessed with the Acromegaly Quality of Life Questionnaire, with increases in quadriceps muscle strength and 6-min walking distance. However, none of these benefits remained when the patient was assessed after a 1-month washout period.
Conclusion: This study showed that patients with acromegaly may benefit markedly from TOHR, which could provide a novel therapeutic approach as an adjunct to hormone control therapy.

1. Introduction

Acromegaly is a rare, chronic, disabling disease of endocrine origin that causes several debilitating systemic dysfunctions due to the excessive production of growth hormone (GH) and insulin-like growth factor I (IGF-I) (Gadelha et al., 2017).

In 98% of cases, the disease is caused by a sporadic somatotropinoma. Sporadic somatotropinomas are tumors of monoclonal origin. A mutation that activates the alpha subunit of stimulatory G protein (sgp) is the most common genetic alteration, and it is found in approximately 40% of patients. Somatrotopinomas include macro- (≥1 cm) and microadenomas (<1 cm); purely GH-secreting tumors (60% of cases), mixed tumors (GH, prolactin, thyroid-stimulating hormone and/or corticotrophin) and occasionally pituitary carcinomas (fewer than 20 published cases); and, even more rarely, hypothalamic neoplasms secreting growth hormone-releasing hormone (GHRH), which stimulates the pituitary gland's production of GH. However, there may occasionally be secondary causes or ectopic sources of excessive GHRH. Typical secondary sources include malignant neoplasms of the adrenals, lungs and pancreas; more rarely, GHRH is secreted by neuroendocrine tumors of the gastrointestinal tract, such as gastrinomas and insulinomas. GH-secreting ectopic tumors (pancreatic islet tumors and non-Hodgkin's lymphoma) occur very rarely (Chanson and Salenave, 2008; Chanson et al., 2009).

* Corresponding author. Rua Araguaia, 1266, Block 1/405, Freguesia, Jacarepaguá, 22745-271, Rio de Janeiro, RJ, Brazil.
E-mail address: agnaldolopes@pq.cnpq.br (A.J. Lopes).

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In a smaller percentage of cases (5%), the disease may be inherited, as is the case with multiple endocrine neoplasia syndromes type 1 and type 4, Carney complex, and familial isolated pituitary adenoma (FIPA), including its subtype, isolated familial somatotropinoma (IFS) (Gadelha et al., 2017; Marques et al., 2017). There are anecdotal reports of the disease being caused by an overdose of GH during treatment for children who do not produce this hormone and in athletes who use GH as a drug to improve muscle performance (Macintyre, 1987; Karges et al., 2004).

Chronic exposure to GH and IGF-I has multisystemic repercussions, with changes in metabolic parameters, body composition, cardiac function, pulmonary function, muscle function and exercise capacity, among other effects (Dantas et al., 2013; Hatipoglu et al., 2014; Volschan et al., 2017). IGF-I is produced primarily by the liver (which is responsible for ≈75% of circulating IGF-I) in response to elevated GH levels and, to a lesser extent, to endocrine stimulation of insulin in the liver (Aguirre et al., 2016). Additionally, IGF-I provides an inhibitory feedback signal for GH secretion in the hypothalamus, stimulating the production of somatostatin in the pituitary (Ohlsson et al., 2009). IGF-I is also produced locally in various body tissues, including cartilaginous cells (Aguirre et al., 2016). The availability of IGF-I is tightly regulated by insulin-like growth factor binding proteins (IGFBPs) (Rajpathak et al., 2009). Elevated levels of IGF-I affect several metabolic pathways, via (1) competition with insulin for the insulin receptor, resulting in diabetes mellitus; (2) general somatic hypertrophy (e.g., macroglossia, cardiomegaly, large kidneys and bulky skeletal muscles); and (3) binding to insulin-like growth factor-1 receptor (IGF-1R), which is a tyrosine kinase receptor that causes the phosphorylation and activation of various intracellular signaling pathways, including the activation of the AKT pathway, resulting in the growth and proliferation of somatic cells (Cruzat et al., 2008; Aguirre et al., 2016; Adigun and Mesfin, 2017).

Many of the clinical manifestations of acromegaly are common to other, more prevalent diseases, and diagnosis is often delayed by approximately 8–10 years after the onset of the first signs and symptoms (Brue and Castinetti, 2016). Adult patients with acromegaly display characteristic features of forehead protrusion, nose and lip augmentation, nasolabial sulcus accentuation, prognathism, and enlarged hands and feet (Adigun and Mesfin, 2017). Acromegaly can lead to visceromegaly, hypertension, arrhythmias, cardiomyopathy, diabetes mellitus, ventilatory dysfunction, sleep apnea, osteoarthritis and compressive neuropathies (Colao et al., 2004; Pivonello et al., 2017). These patients may also present with general fatigue, headache, visual changes, hyperhidrosis, acanthosis nigricans, hypopituitarism, hyperprolactinemia, nephrocalcinosis and an increased incidence of colon and thyroid cancer (Table 1) (Colao et al., 2004). The clinical diagnosis is confirmed biochemically by an elevated IGF-I level for age and a nadir serum GH concentration higher than 1.0 μg/L following an oral glucose tolerance test (Katznelson et al., 2014). The assessment of tumor volume and extent is based on imaging studies using magnetic resonance imaging or computed tomography of the sella turcica (Melmed et al., 2005). The goals of treatment are to correct (or prevent) tumor compression by excision, reduce GH and IGF-I levels to normal, control symptoms, improve quality of life and reduce mortality (Cordido et al., 2013; Leopoldo et al., 2017). Transsphenoidal surgery is the treatment of choice, with exceptions for patients who have a clinical contraindication or who decline the procedure or for cases of almost entirely unresectable tumors (e.g., those with an epicenter within the cavernous sinus) (Katznelson et al., 2014). When surgery fails to correct GH/IGF-I hypersecretion, adjuvant drug treatment is indicated. At present, there are three classes of drugs available for the treatment of acromegaly: somatostatin receptor ligands, dopaminergic agonists, and GH receptor antagonists (Giustina et al., 2014; Katznelson et al., 2014). Radiation therapy is currently proposed as a third-line treatment (Chanson et al., 2009; Leopoldo et al., 2017). The prognosis of acromegaly has improved in recent years. However, even when patients are cured or their disease is well controlled, sequelae often remain (Leopoldo et al., 2017).

There are innumerable functional limitations that negatively affect the ability of patients with acromegaly to perform activities of daily living (ADLs) and contribute to the deterioration of their health-related quality of life (HRQoL). The dysfunctions that occur in acromegaly mainly involve the bones, joints and muscles, and these structures are affected in almost all cases (Lopes et al., 2014; Lopes et al., 2014; Mazziotti et al., 2018). In patients with acromegaly, progressive damage to the articular and musculoskeletal systems occurs, causing temporomandibular joint dysfunction, hypertrophic arthropathy, chrondrocalcinosis, limitations of joint mobility, genu varum, acroparesthesias, carpal tunnel syndrome, thoracic spine kyphoscoliosis, intermittent claudication (lumbar spinal stenosis) and proximal myopathy (Colao et al., 2004; Chanson and Salenave, 2008; Pivonello et al., 2017). Acromegaly is associated with significant alterations in both peripheral muscle strength and endurance; these patients have reduced muscle strength despite the marked muscular hypertrophy described in previous skeletal muscle biopsy studies (Nagulesparen et al., 1976; Guedes da Silva et al., 2013; Lopes et al., 2015). Acromegalic arthropathy affects both the axial and peripheral joints; the knee is the joint most often involved, followed by the shoulder, hip, ankle, elbow and hand joints (Colao et al., 2004; Scacchi and Cavagnini, 2006). Consequently, joint pain had been described in up to 90% of acromegalic patients and negatively impacts their HRQoL (Crespo et al., 2017).

In acromegaly, arthropathy progresses inexorably and unpredictably to advanced stages in smaller ways; it is not influenced by

Table 1
Clinical manifestations and chronic complications of acromegaly.

Craniofacial	Increased skull volume; thickening of the scalp; forehead protrusion; accentuation of the malar bone; enlargement of the nose and ears; pronounced nasolabial folds; thickening of the lips; macroglossia; prognathism; jaw thickening; teeth separation
Upper and lower extremities	Enlarged hands with sausage-like fingers; enlarged feet with increased shoe size
Skin and appendages	Thickening of the skin with accentuated folds and scars; hyperhidrosis; hirsutism; skin tags; acanthosis nigricans
Osteomyoarticular and nervous systems	Temporomandibular joint dysfunction; thickening of articular cartilage; arthralgias; osteoarthritis; hypertrophic arthropathy; chrondrocalcinosis; joint deformity; crackling upon movement; compressive neuropathy; carpal tunnel syndrome; kyphoscoliosis; intermittent claudication; muscle weakness; proximal myopathy
Organomegaly	Cardiomegaly; hepatomegaly; splenomegaly; goiter
Respiratory system	Upper airway obstruction; increased lung volume; ventilatory dysfunction; sleep apnea
Cardiovascular system	Hypertension; left ventricular hypertrophy; arrhythmias; congestive heart failure
Metabolism	Insulin resistance; diabetes mellitus; hypertriglyceridemia; hyperphosphatemia; hypercalciuria; hyperprolactinemia
Tumor compression	Headache; facial pain; visual deficits (quadrantanopsia, hemianopsia and amaurosis); hypopituitarism; non-tumoral hyperprolactinemia
Other	General fatigue; lethargy; nephrocalcinosis; increased risk of colon and thyroid cancer

Adapted from Colao et al. (2004); Melmed et al. (2005); Scacchi and Cavagnini (2006); Adigun and Mesfin (2017); Pivonello et al. (2017).

effective treatment of the disease, except in the case of diffuse joint symptoms and pain at some sites (Chanson and Salenave, 2008; Chanson et al., 2009). In terms of skeletal muscle, two recent studies showed a paradoxical reduction in muscle mass and an increase in proximal muscle fatigue in patients who achieved biochemical control of acromegaly (Bredella et al., 2017; Füchtbauer et al., 2017). However, to the best of our knowledge, no controlled trial has investigated the effects of effective treatment of the disease on muscle function, as determined by measures of skeletal muscle performance. Given the advances in the treatment of acromegaly, it seems appropriate to assess the impact of these costly interventions on physical performance and functional abilities in patients with varying degrees of GH/IGF-I control. Despite the important functional limitations resulting from the involvement of the osteomyoarticular system, rehabilitation programs are not currently recommended for this patient population.

In recent years, HRQoL has been considered as an important factor in the clinical management of acromegaly (Crespo et al., 2017). In these patients, HRQoL is impaired even after clinical treatment and the normalization of the target biochemical values, i.e., GH and IGF-I, which suggests that new therapeutic approaches should be sought to improve functionality (Geraedts et al., 2017; Kyriakakis et al., 2017; Webb et al., 2017). Several investigators have hypothesized the possible benefits of ADL rehabilitation for patients with acromegaly, tracing the profile of changes that occur in this population throughout life and identifying the most important points and the main deficiencies and discomforts reported. However, only two studies have objectively evaluated the contributions of regular physical exercise to the physical and cardiovascular performance of acromegalic patients with the aim of characterizing the importance of physical activity in cases of physical and emotional impairments (Hatipoglu et al., 2014, 2015). Despite these studies, data on physical performance in acromegaly are limited, and physiotherapeutic approaches to such dysfunctions and with their impacts on patient well-being are still poorly established (Dantas et al., 2013; Guedes da Silva et al., 2013; Lopes et al., 2015). We believe that individuals with acromegaly may benefit from a protocol of physiotherapeutic treatment directed towards controlling functional limitations. Thus, the purpose of this case study was to evaluate the effect of therapist-oriented home rehabilitation (TOHR) for a patient with acromegaly.

2. Methods

2.1. Case description

A 53-year-old male with a body mass index of 25.7 kg/m^2 was enrolled in TOHR. He had been diagnosed with primary acromegaly 17 years prior, when he started experiencing severe headaches, arthralgia and enlargement of the hands, feet and face. At that time, the patient underwent computerized tomography of the skull and magnetic resonance imaging of the sella turcica, which revealed a GH-secreting pituitary macroadenoma measuring 1.3 x 1.7 × 1.5 cm, with no evidence of invasion or compression of neighboring structures. The diagnosis of active acromegaly was confirmed based on high levels of IGF-I in the blood (224% above the upper limit of the normal range) and high levels of GH (61.1 μg/L) that were not suppressed to <1 ng/mL following documented hyperglycemia during an oral glucose tolerance test (Katznelson et al., 2014). The patient had enlarged lips, an enlarged nose and forehead, excessive sweating and periarticular edema. He also had a diagnosis of difficult-to-control diabetes mellitus. His personal history included dyslipidemia, degenerative disc disease (DDD) of the lumbosacral spine and amputation of the right 5th toe due to peripheral neuropathy. He had no carpal tunnel syndrome. A transthoracic echocardiogram showed minimal mitral regurgitation, thyroid ultrasonography showed hypoechoic nodules, and colonoscopy showed no alterations.

He underwent transsphenoidal surgery as the primary treatment but was not cured. He was then treated with short-acting octreotide followed by octreotide LAR to a dose of 30 mg every four weeks without achieving disease control. He then underwent radiotherapy (total dose 50 Gy), restarted octreotide LAR afterwards, and achieved disease control (serum levels of GH and IGF-I of 0.39 μg/L and 66% below the upper limit of normal, respectively). Currently, the patient is using octreotide LAR 30 mg every four weeks, in addition to metformin, repaglinide and NPH insulin. The patient was right-handed and complained of difficulty performing tasks involving the hands. He reported pain in his lower limbs and fatigue when he climbed a few flights of stairs. Although he was able to perform ADLs independently, he reported some difficulty or discomfort when performing them. During the physiotherapeutic evaluation, the patient had the following vital signs: blood pressure of 120/80 mmHg, heart rate of 80 beats per minute, respiratory rate of 13 breaths per minute, peripheral oxygen saturation of 98%, and modified Borg scale score of 0. On physical examination, bilateral pain was identified in the upper limbs (specifically in the shoulders) and in the lower limbs (specifically in the legs). The patient presented with thoracic hyperkinesis. The range of motion evaluation showed that the joints were preserved.

2.2. Intervention and outcome

To define the patient's physical activity level, the International Physical Activity Questionnaire (IPAQ) was applied (Matsudo et al., 2001); he was classified as sedentary. To screen for cognitive function, the patient underwent the Mini-Mental State Examination (MMSE) (Brucki et al., 2003), which evaluates spatio-temporal orientation, attention, memory, language, calculation and coordination; the total score for between five and eight years of schooling is 26, and our patient reached the maximum score. The patient was assessed to determine the presence of the following criteria that would exclude him from participating in the intervention protocol: significant limitations due to osteoarthropathy that would prevent him from performing the proposed activities; any orthopedic surgery in the previous year; inability to perform the 6-min walk test (6MWT); significant cognitive alteration; uncontrolled hypertension; use of psychotropic drugs; and the presence of untreated hypothyroidism or hypocortisolism (Hubble et al., 2014). Upon entering the intervention protocol, the patient was evaluated by a cardiologist, a neurologist, a rheumatologist and an endocrinologist to ensure that he did not have any contraindications to exercise.

After a physical therapy evaluation, the patient underwent a booklet-guided physical exercise program that lasted two months (3 times per week with a duration of 60 minutes per session). Activities included overall stretching and strengthening (flexion, extension, adduction and abduction movements) and muscular endurance exercises (exercises involving open and closed kinetic chains), along with aerobic conditioning using a functional circuit (Figs. 1–7). The patient was evaluated at 3 different timepoints (baseline, after 8 weeks of training, and after a 4-week washout period with no treatment); thus, he served as his own control. The physiotherapist contacted the patient by phone weekly to follow the progression of the treatment. Throughout the implementation of the protocol, the patient regularly attended his follow-up visits with the multidisciplinary team. Moreover, there was no change in pharmacological treatment throughout this period.

To measure the results, the patient underwent HRQoL, general fatigue, peripheral muscle strength and functional capacity assessments. HRQoL was evaluated using the Acromegaly Quality of

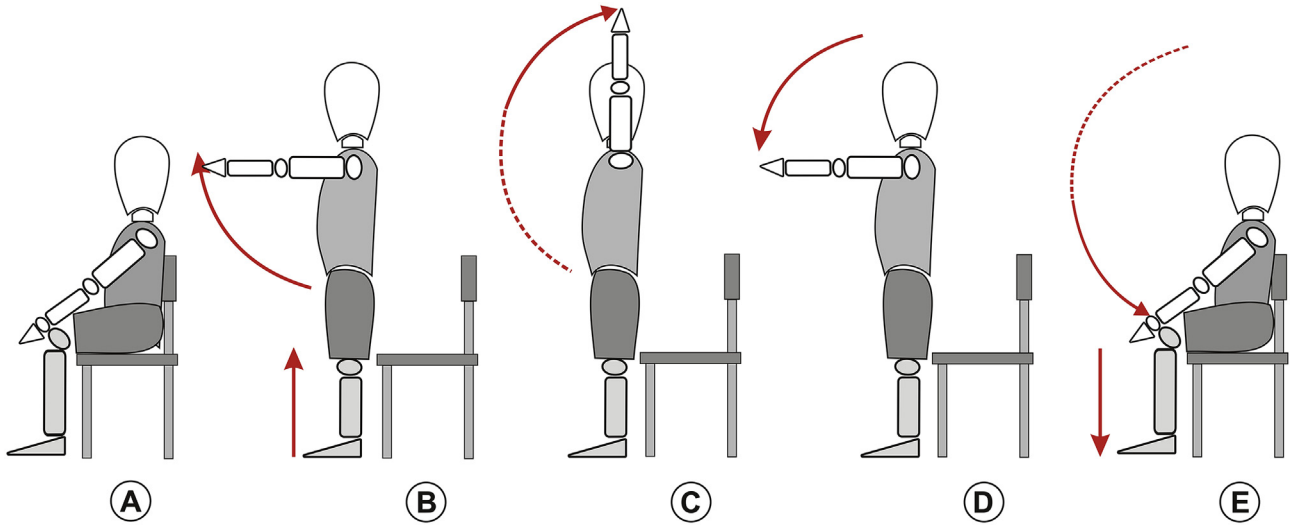

Fig. 1. Strengthening exercises for the arms. The following instructions were given: "Begin in a seated position. Rise from the chair, raising your arms as high as you can, and then sit down slowly, bringing your arms to the starting position. Repeat this exercise 20 times."

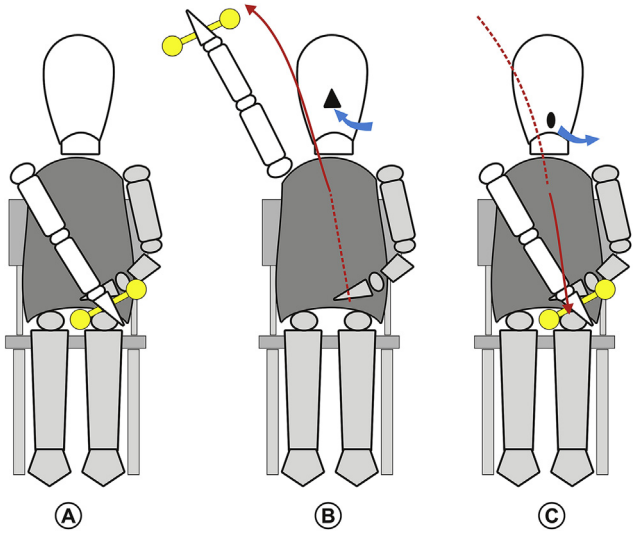

Fig. 2. Strengthening exercises for the arms. The following instructions were given: "Sitting, placing your right hand on your left thigh. Raise your arm diagonally and return to the starting point 20 times. Repeat this exercise with the other arm."

Life Questionnaire (AcroQoL), a simple and validated disease-specific instrument for acromegaly that contains 22 items divided into two scales: one that evaluates physical aspects (eight items) and another that evaluates psychological aspects (14 items) (Badia et al., 2004). Each item on the AcroQoL has five possible answers, and the maximum score of 110 reflects the best possible HRQoL, while the minimum score of 22 reflects the worst HRQoL possible. Overall fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, a specific scale for evaluating fatigue in chronic disease. It comprises 13 questions with responses ranging from 0 to 4; the higher the score, the less general fatigue is present (Randazzo et al., 2017). Hand grip strength was assessed using an isometric hydraulic dynamometer (SH5001, Saehan Corporation, Korea); the patient was instructed to perform three maximum voluntary contractions with an interval of 60 seconds between them; the highest value was then used for the isometric handgrip strength (iHGS) analysis (Neves et al., 2017). Lower limb functionality was assessed using the Lower Extremity Functional Scale (LEFS), a self-administered questionnaire with 20 questions, each of which is scored on a range from 0 (extremely difficult) to 4 points (no difficulty); the sum of all items generates a maximum total of 80 points, and the higher the score is, the better the integrity of the lower limbs (Pua et al., 2009). Quadriceps muscle function was evaluated using an isometric dynamometer (model DIN-TRO, EMG Systems of Brazil LTDA, Brazil); the patient was instructed to cross his arms over his thorax while the seat was adjusted to allow 90 degrees of flexion at the hip joint (Dos Santos et al., 2014). The 6MWT was performed in duplicate with at least 30 minutes of rest between evaluations, using a 30-m corridor with a smooth surface that was marked every 3 m; the step-by-step approach to the 6MWT was recommended in a previous publication (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002).

After the physical therapy follow-up, improvements were observed in several physical and psychological aspects. The results at baseline, after two months of exercise and after 1 month of washout are shown in Table 2. After 2 months of exercise, the patient's HRQoL improved, as shown on the AcroQoL; the patient presented a higher total score and higher scores on the physical, psychological and appearance components, despite the absence of increases in the scores related to interpersonal relationships. There was a considerable increase in quadriceps muscle strength and an increased score on the LEFS scale, which also assesses lower limb functionality. The 6-min walking distance (6MWD) increased considerably after 8 weeks of exercise (90 m), despite only slight improvements in general fatigue as assessed by the FACIT-F. The iHGS showed no differences after the rehabilitation period in either the dominant or the non-dominant hand.

3. Discussion

Functional rehabilitation is the branch of health science that assists in the empowerment of the individual with dysfunction by improving functionality in the presence of abnormalities (Steiner et al., 2002). Despite its importance, functional rehabilitation is still minimally used in cases of acromegaly, where there are usually many limitations, and the treatment is mostly limited to the hormonal control of disease activity (Hatipoglu et al., 2015). In terms of

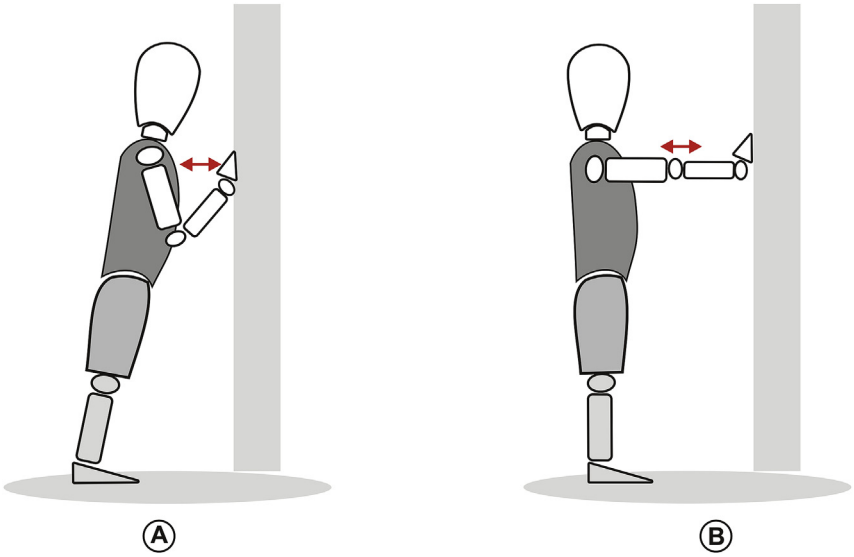

Fig. 3. Strengthening exercises for the arms. The following instructions were given: "Facing the wall, lean forward (as if you are about to fall). Rest your hands on the wall, and bend your elbows. Then, use force to return to the starting position. Repeat this exercise 10 times."

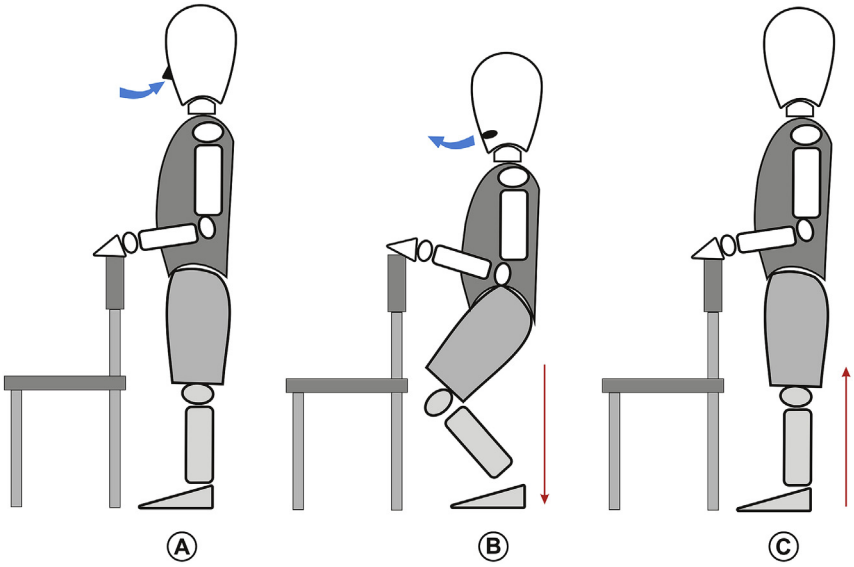

Fig. 4. Strengthening exercises for the legs. The following instructions were given: "Stand behind the chair. Fill your lungs through your nose. Release the air slowly through your mouth as you descend and rise again. Repeat this exercise 20 times."

musculoskeletal and neurological symptoms, our patient suffered intense headaches and arthralgias at the time of diagnosis, having developed DDD of the lumbosacral spine and muscular dysfunction. Thus, we think that early treatment in the form of resection of the hypophysis tumor and biochemical control at least minimized the effects of tumoral compression in the skull and extracranial symptoms of the illness (Chanson and Salenave, 2008). Our patient had good adherence to the rehabilitation program; he performed all the exercises specified by the physiotherapist and completed all the scheduled exercise sessions. It is worth noting that we evaluated the impact of TOHR as an adjunctive measure; we did not make any changes to either the medical treatment that the patient was receiving or to his lifestyle beyond the exercises.

Muscle dysfunction is present in many acromegalic patients (Colao et al., 2004; Lopes et al., 2015). Our patient showed a baseline quadriceps muscle strength value that was slightly above the median described in the sample evaluated by Guedes da Silva et al. (2013), suggesting that he did not have a severely disabling muscular disease. After 2 months of exercise, quadriceps muscle strength increased by 30%; however, a 20% drop was detected during the washout period, suggesting the importance of maintaining rehabilitation in this patient population. More recently, a study evaluated the role of regular exercise in muscle function in a population of patients with acromegaly using handgrip and the sit and reach test (SRT) to assess muscle strength and flexibility, respectively (Hatipoglu et al., 2015). The study group exercised 3 days a week for 3 consecutive months, and each 75-min exercise session consisted of warm-up, cardio, strength, balance, and stretching exercises. After 3 months of exercise, Hatipoglu et al. (2015) observed an increase in SRT compared with baseline values ($P = 0.004$), although they did not notice any significant changes in handgrip, as seen in our study. It is worth noting that

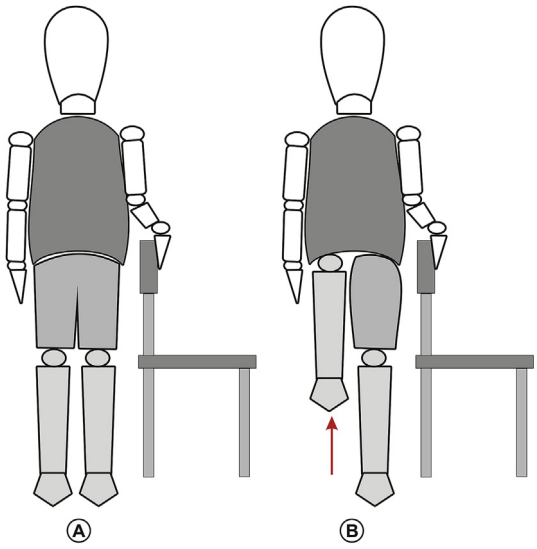

Fig. 5. Strengthening exercises for the legs. The following instructions were given: "Standing up and using the back of a chair to balance, raise your knee as high as you can and then lower it. Repeat this exercise 20 times and then repeat with the other leg."

despite similarities in the protocols of the two studies, our study used TOHR, while the study by Hatipoglu et al. (2015) used a regimen that was directly supervised in the hospital (outpatient). Several studies have shown that hospital (outpatient) and TOHR exercise training programs are equally effective at improving exercise capacity and HRQoL in several clinical conditions, although TOHR offers the advantages of better adherence and a shorter period (Clawson et al., 2018; Su et al., 2017; Wuytack et al., 2017).

In our study, the differences in the observed results among the muscle groups targeted by the physiotherapeutic approach can be explained by the fact that the musculature of the hands and arms is subject to complications of acromegaly (such as carpal tunnel syndrome and swelling of the hands and fingers), which compromises the results of rehabilitation (Füchtbauer et al., 2017). Interestingly, in acromegaly, there is hypertrophy of the type I fibers and atrophy of the type II fibers, which generates significant functional alterations and reductions in muscle strength and endurance (Nagulesparen et al., 1976; Miller et al., 2008; Guedes da Silva et al., 2013). This is because the size of the muscle fibers does not translate into strength gain, and as a result, there is a significant deficit in muscle function (Miller et al., 2008; Guedes da Silva et al., 2013). In addition to the intrinsic changes in muscle fibers, other factors also contribute to peripheral muscle weakness in this condition, including the direct effect of GH and IGF-I on the muscles, the physical inactivity inherent to the disease and the metabolic changes associated with the disease, such as hypothyroidism, hypoadrenalism and diabetes (Colao et al., 2004; Guedes da Silva et al., 2013; Walchan et al., 2016). Although GH promotes protein synthesis, it increases fluid retention without any improvement in muscle mass or strength; however, IGF-I participates in the formation, maintenance and regeneration of the musculoskeletal system and contributes to the proliferation of myoblasts, myogenic differentiation and muscular hypertrophy (Fernandez and LeRoith, 2005; Freda et al., 2009). Moreover, there are still significant joint alterations that negatively impact the performance of the musculoskeletal system. Enlargement of the joint spaces, the formation of osteophytes, bone proliferation at the sites of tendon fixation and deposits of periarticular calcium on the surface of the bone have been reported; in the more advanced stages of acromegaly, there is narrowing of the joint spaces, osteophytosis and bone cyst formation (Scacchi and Cavagnini, 2006; Chanson and Salenave, 2008; Killinger et al., 2012). These changes culminate with the thickening and overgrowth of cartilage, making patients more prone to the development of secondary osteoarthropathy and joint instability, especially in joints that support more weight.

More than 50% of patients with acromegaly exhibit altered glucose metabolism at diagnosis, which may persist if acromegaly is not controlled (Alexopoulou et al., 2014; González et al., 2018). GH-induced insulin resistance, impairment of β-cell function and increased gluconeogenesis are considered to be the major mechanisms accounting for glucose intolerance in patients with acromegaly (Alexopoulou et al., 2014; Hannon et al., 2017). Our patient had difficult-to-control diabetes mellitus prior to rehabilitation, which may have contributed to his osteomyoarticular dysfunction (Colao et al., 2004; Guedes da Silva et al., 2013). Upon entering the

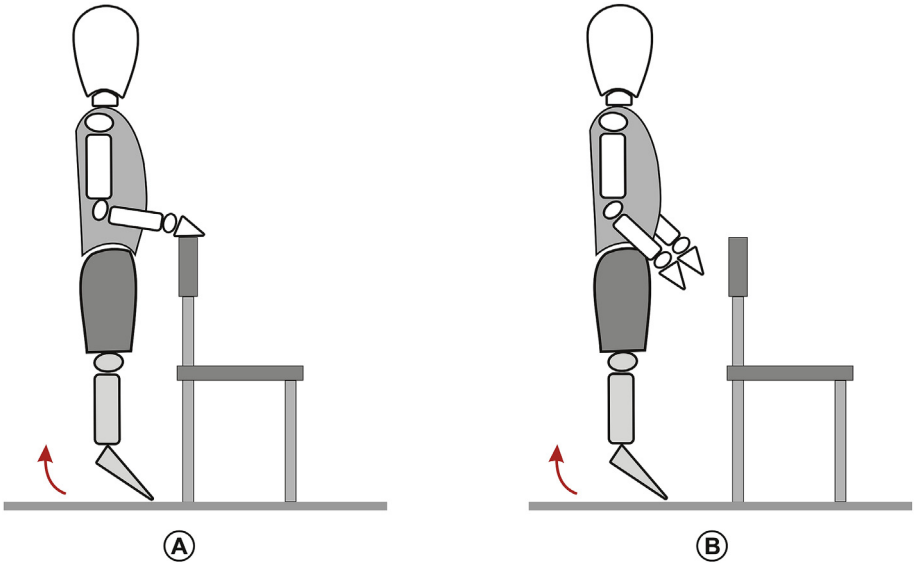

Fig. 6. Strengthening exercises for the legs. The following instructions were given: "Stand on your tiptoes and descend slowly. Try to do so without support. If it gets difficult, you can support yourself with one finger, one hand or both hands, but use the least support necessary. Perform 3 sets of 15 repetitions each."

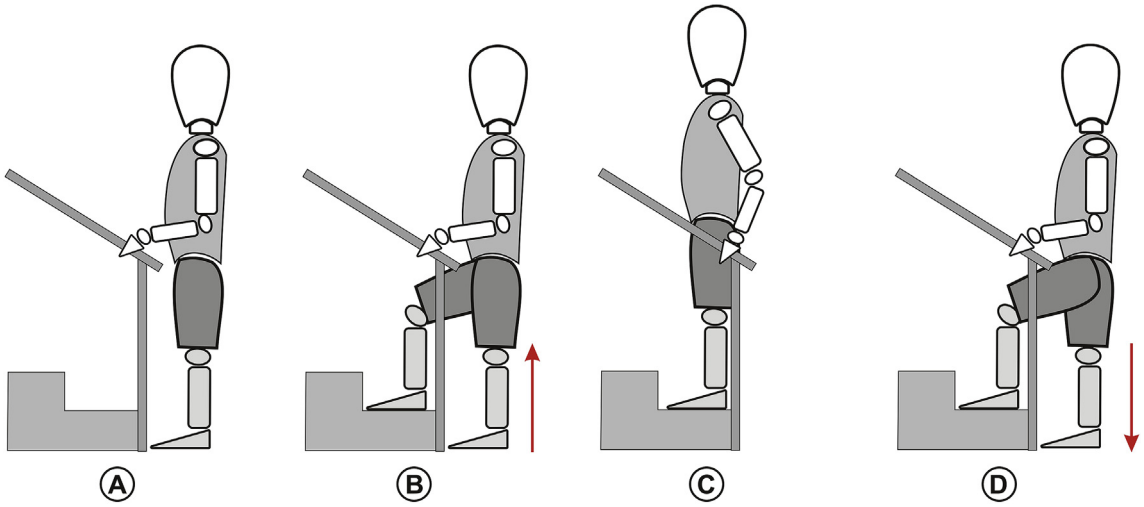

Fig. 7. Strengthening exercises for the arms. The following instructions were given: "Stand facing a step where you have support for your safety. Go up and down this step 20 times, starting with the right leg. Then, repeat, starting with the left leg."

Table 2
Parameters assessed during therapist-oriented home rehabilitation.

Variable	Baseline	After 2 months of exercises	After 1 month of washout
AcroQoL			
Total score (points)	55.6	62.5	54.5
Physical performance (points)	62.5	65.6	59.3
Psychological well-being (points)	51.7	55.4	51.8
Appearance (points)	39.2	50.0	35.7
Personal relationships (points)	64.2	60.7	67.9
FACIT-F (points)	30	31	29
iHGS			
Right hand (kgf)	37	37.1	37
Left hand (kgf)	30.8	30.6	30.3
LEFS (points)	73	75	72
Quadriceps muscle strength (kg)	48.7	62.9	50.7
Six-minute walking distance (m)	332	422	380

AcroQoL, Acromegaly Quality of Life Questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; iHGS, isometric handgrip strength; LEFS, Lower Extremity Functional Scale.

intervention protocol, however, his acromegaly was controlled, and he had normal glucose levels. Since rigorous glycemic control was maintained throughout the duration of the physical therapy program (data not shown), we attributed the improvements only to physical therapy.

The 6MWT is considered a good test to use with acromegaly patients in clinical practice; in addition to being easy to administer and inexpensive, it provides a submaximal measure that satisfactorily reflects the individual's limitations in ADLs (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002; Lopes et al., 2015). After 2 months of physical exercise, our patient showed a 90-m increase in 6MWD, which was well above the minimal clinically important difference (MCID) reported in healthy older adults, which is approximately 50 m (Perera et al., 2006). As with quadriceps muscle strength, it is important to note that the values that our patient achieved did not persist after the 1-month washout, which highlights the importance of maintaining regular physical activity in this patient population. Interestingly, when Hatipoglu et al. (2015) examined the effects of 3 months of regular physical exercise in 11 patients with acromegaly and evaluated exercise tolerance using ergometry, they found increases in maximal oxygen uptake and in the time taken to complete the Bruce protocol ($P = 0.003$ and $P = 0.004$, respectively), in addition to a reduction in heart rate during warm-up for the test ($P = 0.04$), relative to baseline values. However, the authors did not investigate the impact of rehabilitation on ADLs and patients' functionality and thus failed to propose any recommendations regarding appropriate levels of physical activity for this population. These results point to an improvement in functional capacity after a period of exercise, whether evaluated through a submaximal test (which is the case for our patient) or a maximal test as evaluated by Hatipoglu et al. (2015). In acromegaly, several changes may be involved in reduced functional capacity beyond decreased peripheral muscle strength and endurance, including other conditions, such as arthropathy, metabolic abnormalities, cardiovascular disease and respiratory dysfunction (Colao et al., 2004). In these patients, arthropathy is undoubtedly the most important cause of morbidity and functional disability, caused by both direct action of the GH/IGF-I axis and secondary degenerative changes (Colao el at., 2004; Killinger et al., 2012). Another aspect that should be considered involves the acromegaly related changes in general fatigue and the integrity of lower limbs. Homem et al. (2017) and Lopes et al. (2015) investigated fatigability and functionality and observed a propensity for general fatigue among these individuals. Our patient presented slightly better FACIT-F and LEFS scores soon after the end of the exercise program, although these values may be below the MCID expected for patients with acromegaly. A possible explanation for the discrete changes in the FACIT-F and LEFS scales

may be the subjective nature of these measures, in contrast with the isometric dynamometer and the 6MWT, which provide objective measures.

The impact of acromegaly on HRQoL has been increasingly discussed. Acromegaly causes many physical dysfunctions and psychological changes that inevitably affect HRQoL (Crespo et al., 2017). Although acromegaly patients show a more impaired HRQoL when the disease is active, some studies have detected losses in HRQoL despite long-term biochemical remission, and much of the HRQoL deterioration was explained by impaired physical function (Biermasz et al., 2004; Tiemensma et al., 2011; Kyriakakis et al., 2017). Aspects such as pain, reduced muscle strength, altered body image and depression strongly influence the perception of HRQoL, and consequently, these patients have great restrictions in ADLs (Webb et al., 2002; Miller et al., 2008). More recently, Chin et al. (2017) found that medical treatment with octreotide over a 24-week period in 58 patients with acromegaly had a limited impact on HRQoL, as assessed with the AcroQoL. Taken together, these findings indicate that new therapeutic approaches may be important as adjuvant methods for improving the HRQoL of patients with acromegaly.

In our case study, the patient showed a 6.9-point improvement in the total AcroQoL score after 2 months of physical exercise; this value was above the MCID reported by Caron et al. (2016), who determined the MCID in a cohort of acromegalics based on a change in the total AcroQoL score (improvement) of >50% of the baseline standard deviation. Interestingly, Hatipoglu et al. (2014) investigated the effects of 3 months of regular physical exercise (warming up, cardio, strength, balance and stretching) on HRQoL, self-esteem, body perception and depression. Similar to our findings, they observed a higher total AcroQoL score in their cohort of 11 patients after 3 months of exercise; the patients' median score increased from 64 to 74 points, although the change was not statistically significant ($P = 0.2$). In addition, Hatipoglu et al. (2014) observed improvements in specific aspects of the AcroQoL. When we evaluated the specific domains of the AcroQoL in our patient, we observed that the physical and mental components demonstrated increased scores after the therapeutic approach but returned to baseline after the 1-month washout period.

A critical analysis of the limitations of this case study is warranted. First, case studies are particularly weak within the hierarchy of research because the information they provide has not been tested using rigorous scientific means; however, case studies are informative and relevant to the area of clinical practice from which they originate (Bolton, 2014). Second, case studies are characterized by a single-study design, anecdotal data collection and lack of statistical analysis. Third, we did not perform knee isokinetic dynamometry, which is the gold standard for the assessment of peripheral muscle function (Neil et al., 2013). Finally, the evaluation of exercise tolerance with a cardiopulmonary exercise test could provide more reliable measurements of the benefits of TOHR (American Thoracic Society and American College of Chest Physicians, 2003). Despite these limitations, this case study can serve as a starting point for the design of longitudinal studies to establish the strength of recommendations for physiotherapeutic rehabilitation in a large number of patients with acromegaly, whether active or controlled.

4. Conclusion

The present case study shows that patients with acromegaly may benefit significantly from TOHR. Considering the current advances in functional rehabilitation, it is critical to identify its importance in this group of patients and its long-term benefit as an adjuvant to hormonal control therapy.

Conflicts of interest

The authors would like to disclose that there is no conflict of interest associated with producing this case report.

Ethical guidelines

The entire protocol followed the recommendations for human research provided in the Declaration of Helsinki. The patient signed an informed consent form, which was previously approved by the Research Ethics Committee of the Augusto Motta University Center under number CAAE-53384316.6.0000.5235.

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