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Case report

Human growth hormone stabilizes walking and improves strength in a patient with dominantly inherited calpainopathy

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Abstract

The aim was to investigate if daily low-dose treatment with recombinant human growth hormone (somatropine) can stabilize or improve muscle strength and walking capability in a patient with dominantly inherited calpainopathy. The patient was treated with daily injections of somatropine, except for a 6-month pause, over a period of 4.5 years. Efficacy was assessed by repeated muscle dynamometry tests and 6-minute walk tests (6MWT). Strength improved in most muscle groups on treatment, deteriorated in the 6-month off treatment, and improved again when treatment was resumed. The 6MWT stabilized during the initial 18-month treatment period, then deteriorated in the 6 months off treatment and improved to pre-trial levels when treatment was resumed.

The findings suggest that supplementation with somatropine, within physiological ranges, may improve muscle strength and stabilize walking capability in a patient with calpainopathy. This finding calls for testing of somatropine supplementation in muscular dystrophies in a randomized study.

Keywords: Limb girdle muscular dystrophy; Calpainopathy; Human growth hormone

1. Introduction

Limb-girdle muscular dystrophies (LGMDs) encompass a genetically and clinically heterogeneous group of rare muscle disorders. They are characterized by progressive muscle wasting, most often affecting hip girdle muscles first. Autosomal recessively inherited calpainopathy (LGMD2A) is the most common subtype of LGMD world-wide, and is caused by mutations in the *CAPN3* gene located on chromosome 15q15.1-15.3 encoding calpain-3, a calcium dependant protease [1–3]. Recently, it was reported that calpainopathy also exists in an autosomal dominant form, producing muscle wasting and weakness in similar muscle groups as seen in the recessive form [4].

Disease-specific, non-experimental treatments for muscular dystrophies are unavailable at present. In the absence of disease-specific therapies for muscular dystrophies, several more general treatments, aimed at boosting muscle regeneration and growth, have been studied. These include treatment with anti-myostatin in Duchenne muscular dystrophy (DMD), facioscapulohumeral dystrophy, and LGMD [5,6], and ongoing trials with similar drugs in inclusion body myositis, LGMD type 2I, Becker and DMD [7,8]. Despite the remarkable side effects, the effect of anabolic steroids on muscle mass and strength has been tested in DMD [9,10]. Likewise, the anabolic effect of insulin-like growth factor 1 (IGF-1) is currently under study in Kennedy disease [11]. Another anabolic compound, human growth hormone (GH), has been studied in a 3-month randomized trial in Becker and DMD [12]. The study was primarily targeted at treating heart failure, and showed improvements in heart function with treatment. Skeletal muscle function was not assessed in detail, but did not seem to change in the 3 months of treatment.

GH is a peptide hormone that stimulates cell growth, reproduction and regeneration via stimulation of IGF-1 synthesis. It increases muscle mass and decreases fat mass through its lipolytic effect [13]. The recombinant form of the hormone (rhGH) is widely used in treatment of patients with GH insufficiency, short stature, renal failure, and Prader–Willi syndrome [14,15]. In line with the idea that IGF-1 can increase muscle strength and function in Kennedy disease [11], and encouraged by the positive effect of rhGH on cardiac failure in Becker and DMD [12], we hypothesized that the anabolic effect of GH can improve muscle strength and walking capability

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in patients with muscular dystrophy who have IGF-1 in the lower normal range, but without GH-deficiency. In the current open-labelled pilot study, we report a beneficial effect of treatment with rhGH in a patient with calpainopathy.

2. Case report

2.1. Patient

A 67-year-old Danish woman was diagnosed with LGMD at age 56 years. A few years earlier, she had experienced premature fatigue, a waddling gait, and loosing strength in her arms. Her primary concern, however, was lower back pain, which led to an MR scan, which showed an almost complete replacement of her paraspinal muscles by fat. She was then referred to our Neuromuscular Clinic. Muscle biopsy showed chronic myopathy and loss of calpain 3 expressions to 5% of normal on western blotting. Creatine kinase levels were 677 U/L (normal <150). Genetic testing revealed a single 21-bp deletion of *CAPN3* (c.643_663del21), which confers a recently described dominantly inherited form of calpainopathy, leading to LGMD [4].

A few years after diagnosis, the patient was considerably disabled and was granted early retirement. With lack of effective therapeutic possibilities, and after finding that the patient had serum levels of IGF-1 in the lower normal range, we hypothesized that daily rhGH supplementation could have a beneficial effect on her physical function despite sufficient GH production. This report therefore describes an open-labelled treatment with rhGH in this patient.

2.2. Treatment and test sessions

The patient was treated over a period of 4.5 years, interrupted by a period of 6 months without treatment after the first 1.5 years of treatment. Before treatment with rhGH, the patient was tested twice with a hand-held dynamometer (CITEC, Holland) to measure muscle strength in upper and lower extremities (see Fig. 2 for muscle groups tested) and with a 6-minute walk test (6MWT) to measure her walking ability. These outcome measures would likely reflect an anabolic effect on muscle function and were chosen as primary and secondary endpoints, respectively.

Prior to treatment, an insulin tolerance test (ITT), to clarify if the patient had GH deficiency, and an oral glucose tolerance test (OGTT) were performed. The patient then started treatment with daily injections of Somatropine 0.2 mg. She came for regular assessments approximately every 3–6 months, where serum IGF-1 was measured and Somatropine dosage adjusted, so that IGF-1 was kept in the upper normal range. After the first 3 months, the Somatropine dose was increased to 0.4 mg daily. At each assessment, the following tests were performed: a 6MWT, muscle dynamometry, an OGTT, an ACTH test, serum pituitary hormones, a DEXA scan and evaluation of major organ functions such as liver, kidney, haematology, lipids, blood glucose and an electrocardiography. The 6MWT was performed according to the American Thoracic Society guidelines [16]. Muscle dynamometry was performed after each of the 6MWT sessions, after a 30-min rest period. For consistency, the same investigator performed all 6MWTs and muscle dynamometry tests.

Written informed consent for all procedures and treatments was obtained from the patient, and the study followed institutional guidelines and the Helsinki declaration.

3. Results

3.1. Pre-treatment measures

Prior to treatment, normal adrenal and thyroid function and postmenopausal hypothalamic-pituitary-gonadal axis were confirmed. IGF-1 was in the lower normal range (94 µg/L). The ITT and OGTT showed a normal response in GH, insulin, C-peptide and glucose. And a DEXA-scan revealed normal bone mineral density and a body fat percentage of 46 (Table 1).

3.2. Primary outcome measures

3.2.1. Muscle dynamometry (Fig. 1)

The improvement in muscle strength after treatment varied among the different muscle groups, and could mostly be explained by the size of the muscle group involved. However, the pattern of response was quite even across muscle groups. Muscle strength increased above pre-treatment levels from test sessions 3 to 8, during rhGH treatment. Strength decreased to baseline levels in the 6-months off treatment period, and remained low in the first months after resuming treatment again (test sessions 9–11). After this, muscle strength increased above baseline and remained elevated during the following 23 months of treatment (test sessions 11–14).

3.3. Secondary outcome measures

3.3.1. 6-Minute walk test (Fig. 2)

Walked distance ranged from 196 to 360 metres. In the first 1.5 years of treatment, walked distance remained stable, but decreased markedly in the 6 months off treatment. Treatment with somatropine was then resumed for another two years, where walking distance, after 6 months, again increased above baseline level (360 m) and then declined to baseline levels in

Table 1
DEXA-scanning and serum IGF-1 levels.

Test session	0	1	4	5	6	7	8	9	10	11	12	13	14
Week	−36	0	14	27	38	47	87	116	133	144	157	180	244
Treatment	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Serum IGF-1 (50–200 µg/L)	94	123	218	183	195	213	156	116	225	138	163	122	134
% Fat on DEXA scan		46	47	45	44	48	49	49	50	47	51	50	45.5
Body weight (kg)		82.7	85.3	88.3	90.3	88.7	95.8	94.7	95.5	93.8	93.1	93.3	93.1
BMI		29.5	30.4	30.4	32.3	31.7	34.2	33.8	34.1	33.5	33.3	33.3	33.1