Muscular force is reduced in neurofibromatosis type 1

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Abstract

Objectives: To measure muscular force in neurofibromatosis type 1 (NF1) patients. Methods: The maximal voluntary muscular force (Fmax) was measured in the first 21 volunteer patients without acute health problems at the routine annual examination in the Neurofibromatosis Outpatient Reference Center during October-November (2007). The NF1 individuals were 9 males and 12 females, aged from 7 to 60 years and physically sedentary. The healthy control group was 21 healthy subjects matched to NF1 group by age, sex and physical activity. A handgrip test instrument was used to measure maximal force. To allow comparisons between physically different patients, forearm circumference (cm) was measured with a tape and forearm cross sectional area was derived to express the force per unit of forearm area. Data were compared using a t Student test (P<0.05). Results: The mean Fmax of NF1 male (260±136 N) and NF1 female (217±76 N) were lower than expected for their sex and age. Healthy men showed greater Farea (9.8±3.2 N.cm⁻²) than NF1 men (5.7±2.6 N.cm⁻²) and healthy women (6.7±1.6 N.cm⁻²) showed greater Farea than NF1 females (5.7±1.9 N.cm⁻²). Conclusion: Maximal voluntary muscle force was reduced in NF1 patients.

Keywords: Neurofibromatosis Type 1, Muscular Force and Handgrip

Introduction

Neurofibromatosis Type 1 (NF1) is a common autosomal-dominant disease (1:3000) with a wide variety of clinical features. Fine motor coordination deficits have been demonstrated in NF1¹. Muscular hipotony was clinically suspected in many of the NF1 patients attended at the Neurofibromatosis Reference Center². However, muscular force has not been quantified in NF1 based on an extensive review of the literature from 1956 to 2008. A previous study using peripheral quantitative tomography showed decreased muscle cross-sectional area plus decreased bone strength in NF1 patients but the muscular force was not measured³. The handgrip force test measures maximal voluntary muscular force (Fmax) and it has successfully been used to evaluate long-term human disability⁴. It is well known that muscular force is correlated to muscle and body dimensions, which varies between males and females, as well as with habitual physical activities and through out the life. To allow comparisons between such different individuals, the handgrip Fmax must be divided by the forearm cross sectional area⁵. Based on clinical observations we hypothesized that Fmax measured by handgrip test would be reduced in NF1 patients.

Material and methods

The Federal University of Minas Gerais Ethical Committee approved this study (# 570/07). The maximal voluntary muscular force (Fmax) was measured in the first 21 NF1 patients and 21 healthy controls. The NF1 individuals were 9 males and 12 females, aged from 7 to 60 years old, without acute healthy problems and physically sedentary. The patients enrolled in this study were volunteers recruited from the annual routine examination in the Neurofibromatosis Reference Center along the period of October and November 2007. The healthy control group was matched by sex, age and physical activity and it was formed by students and university’s workers. The diagnosis of NF1 was established according to the National Institute of Health consensus criteria⁶ and they presented the common clinical features.

The authors have no conflict of interest.

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from minimal to moderate severity according to Riccardi classification\(^7\). The patients with neurological or muscular impairment were excluded from the study. All patients and volunteers signed the informed consent protocol and had their \(F_{\text{max}}\) (N) measured using a 0-100 kg handgrip test instrument (Kratos\(^8\), Brazil). The volunteers were seated during measurements and they were invited to attain their maximal handgrip force for 3 times in each hand and the mean was recorded. The forearm circumference (cm) was measured with a tape at the proximal third and was derived the forearm cross sectional area (cm\(^2\)*4\(\pi\))\(^{-1}\). The force per unit of forearm area (F\(_{\text{area}}\)) was calculated (N/cm\(^2\)). Since there was not statistical difference between right and left forearm forces, the mean force of the two limbs was used for statistical purposes and data were compared between groups using a \(t\) Student test (P<0.05).

### Results

Table 1 presents the mean physical characteristics and the comparisons between the variables measured. The mean \(F_{\text{max}}\) of healthy volunteers were 488±178 N for men and 285±73 N for women and these results ranged between the normal expected values for their sex and age\(^8\), which indicate that the method was useful for the purpose of the present study. However, the mean \(F_{\text{max}}\) of NF1 male (260±136 N) and NF1 female (217±76 N) were lower than expected for their sex and age. Most of the healthy matched volunteers (67\%) presented a greater individual \(F_{\text{max}}\) than NF1 patients (Figure 1).

Healthy individuals of both sexes presented greater mean F\(_{\text{area}}\) than NF1 patients. Healthy men showed greater F\(_{\text{area}}\) (9.8±3.2 N.cm\(^2\)) than NF1 men (5.7±2.6 N.cm\(^2\)) and healthy women (6.7±1.6 N.cm\(^2\)) showed greater F\(_{\text{area}}\) than NF1 females (5.7±1.9 N.cm\(^2\)). As expected, the healthy group showed males with greater F\(_{\text{area}}\) than female, but there was no difference in F\(_{\text{area}}\) between and NF1 male and female patients (Table 1 and Figure 1).

### Discussion

The original finding of the present study is that NF1 patients showed reduced muscular force when compared with matched healthy volunteers. The muscle weakness could be related to the intrinsic genetic and neurological abnormality, already described in NF1, which leads to inefficient neural motor coordination and/or activation\(^1\). Fifty-four percent out of our patients presented clinically observed learning difficulties and cognitive deficits\(^2\), but the number of subjects in the present study was not enough to establish a correlation between learning and cognitive deficits and the observed reduced force.

It is also possible that because of unsightliness, patients with cutaneous neurofibromas tend to remain indoors, which could reduce their daily physical activity resulting in chronic unloading of the forearm and reduced muscular force\(^9\).

Another possible cause of the reduced muscular force observed in NF1 patients could be the calcium metabolism,
which is related to the vitamin D levels. Specific receptors for vitamin D have been identified in human muscle tissue and cross-sectional studies showed that elderly persons with higher levels of vitamin D serum levels have increased muscular force and a lower number of falls. Lower serum 25-OH-vitamin D levels have been previously reported in NF1 patients and correlated with the number of neurofibromas and bone abnormalities. These findings lead us to measure 25-OH-vitamin D and calcium levels in a subsequent volunteered group of NF1 patients (n=27) and healthy controls (n=16). The preliminary result showed that NF1 patients have mean sub optimal levels of serum 25-OH-vitamin D, according to the recent criteria for vitamin D deficiency (ideal>50 ng.dL⁻¹), but there was not difference between NF1 (29.4±10.0 ng.dL⁻¹) and healthy volunteers (25.6±9.3 ng.dL⁻¹).

Interestingly, the NF1 patient’s plasma calcium levels (total: 9.8±0.6 and ionic 4.9±0.2 mg.dL⁻¹) were higher than healthy individuals levels (total: 9.5±0.4 and ionic 4.7±0.1 mg.dL⁻¹) (P=0.02 and P=0.01, respectively). Moreover, in the NF1 group, the patients with lower force showed increased total calcium levels (10.1±0.5 mg.dL⁻¹) compared to those with higher force (9.5±0.6 mg.dL⁻¹) (P=0.01). However, there was not significant correlation between force and calcium levels or force and 25-OH-Vit D levels. These results suggest a possible calcium participation in the mechanism of reduced force in NF1 patients.

Finally, the NF1 male patients showed a greater force reduction (47%) than female patients (24%) compared to its healthy counterparts. These results corroborate a gender-related impact of NF1 pointed previously, but it has not been stressed in the most comprehensive guidelines.

In conclusion, the present study suggests that reduced muscle force could be part of the complex clinical features of NF1 disease, but the causal mechanism of the force reduction remains unknown and deserves further investigation.

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References