Muscle Cramps Profile among Spinocerebellar Ataxias

Spinocerebellar ataxies (SCAs) constitute a heterogeneous group of neurodegenerative disorders, with an autosomal dominant inheritance. More than 40 different SCAs have already been identified, and SCA3, SCA2, and SCA1 are the most frequent types.[1] The most common symptom is cerebellar ataxia, but other clinical manifestations may occur, suggesting a specific mutation that could further guide the genetic testing, such as “bulging-eyes” and upward gaze palsy in SCA3, seizures in SCA10, among others.[1-3]

Muscle cramps, defined as a painful and sustained muscle contraction affecting a muscle or a group of muscles, are a prevalent non-motor symptom in specific SCA subtypes.[3-5] Damage to the lower motor neuron is commonly implied, which causes collateral reinnervation giving rise to intramuscular nerve endings.[5] Although some studies have associated muscle cramps to SCAs, there is no precise information about this symptom among the different types of SCAs.[1-8] In this way, the present study aimed to evaluate the prevalence of muscle cramps and their clinical aspects among the SCAs.

Sixty-eight patients, genetically diagnosed with SCA, were evaluated in the Ataxia Outpatient Clinic of Federal University of Paraná. Participants were divided in four groups according to their SCA subtype: Group 1-SCA2, Group 2-SCA3, Group 3-SCA10, Group 4-“other”, which included patients with SCA1, SCA6 and dentatorubropallidoluysian atrophy (DRPLA). The Scale for Assessment and Rating of Ataxia (SARA) was used for evaluation of ataxia severity.[9,10] Cramps were assessed by a questionnaire regarding patient’s perception. Pain perception was evaluated using the visual analogue scale (VAS).[10]

The Fischer exact test or Chi Square was used to compare qualitative variables. The t Student test was used to compare continuous variables with normal distribution, and the Mann-Whitney test and the Kruskal-Wallis test were applied to compare non-normal continuous variables. Spearman’s coefficient was used for correlations. *P values less than 5% were considered significant (p < 0.05).

All the 68 patients assessed were grouped in each of the following: Group 1 - SCA2 (n = 18; 22.8%), Group 2 - SCA3 (n = 24; 30.4%), Group 3 - SCA10 (n = 19; 24.0%), and Group 4 - “others” (n = 7; 8.9%)[Table 1]. The group “others” was composed by 5 SCA1 patients, 1 SCA6 patient and 1 DRPLA patient. Groups were similar regarding gender, age, disease duration and SARA score [Table 1].

Muscle cramps were present in all patients in the SCA2 group, in 17 patients (70.8%) in the SCA3 group, in 5 patients (26.3%) in the SCA10 group, and in 4 patients in group 4. The SCA2 group, when compared to the other groups (SCA2 vs. SCA3 [p = 0.014]; SCA2 vs. SCA10 [p = 0.0001]; SCA2 vs. “others” [p = 0.015]) showed a significantly higher frequency of muscle cramps. The SCA3 group had a significant higher frequency of muscle cramps compared to the SCA10 group [p = 0.0058] [Table 2].

When comparing the muscle cramps profile between the two most affected groups, SCA2 and SCA3, muscle cramps arose significantly earlier in SCA2 patients (29 ± 12.3 vs 43.2 ± 16.6, P =0.03). There was no difference between frequency, pain perception, duration and the quantity of affected muscle groups. The most affected muscle groups in the SCA2 group were lower limbs (94.4%), neck (44.4%), upper limbs (38.9%) and abdomen (33.3%). Among SCA3 patients the most affected sites were lower limbs (82.3%) and superior limbs (23.5%).

The time of muscle cramps tended to correlate with VAS in the SCA2 group (rho =0.562, P=0.056), but with no statistical

| Table 1: Comparison between patients from different groups |
|---------------------------------|------|------|-----|------|
|                               | SCA 2  n=18 | SCA 3  n=24 | P* | SCA 10 n=19 | Others n=7 |
| Age (years)                   | 47.7±11.5 | 46.7±15.5 | 0.857* | 48.4±9.7 | 56.1±8.1 | 0.433* |
| Gender                        | Female | Male | 0.34* | 10 (55.6%) | 9 (37.5%) | 10 (52.6%) | 4 (57.1%) | 0.602* |
| SARA                          | 15.8±10.2 | 15.7±9.3 | 0.529* | 10.9±6.55 | 11.9±5.6 | 0.311* |
| Age of onset                  | 33.6±9.8 | 35.7±11.7 | 0.435* | 32.0±8.1 | 41.4±8.5 | 0.113* |
| Disease duration              | 12.5±12 | 10±11.5 | 0.368* | 10±20.5 | 15±10 | 0.752* |
| Muscle cramps                 | 18 (100%) | 17 (70.8%) | 0.014* | 5 (26.3%) | 4 (57.1%) | 0.0001* |
| Time since muscle cramps (years) | 16.4±10.3 | 5.5±6.8 | 0.0093* | |
| AOMC (years)                  | 32.5±17.3 | 40.3±21.8 | 0.03* | |
| Frequency (monthly)           | 8±57.25 | 22.5 | 0.818* | |
| Muscle groups (No)            | 2±3 | 1±1.5 | 0.1415* | |
| Cramps’ duration (min)        | 0.46±2.83 | 0.33±0.66 | 0.379* | |
| VAS                           | 5.5±2 | 7±2 | 0.147* | |

SARA scale for the assessment and rating of ataxia; AOMC age of onset of muscle cramps, VAS visual analogue scale for pain. *P values for the comparison between SCA2 and SCA3 groups. **P values for the comparison between all groups. (a) non-parametric Mann-Whitney Test; P<0.05, (b) non-parametric Kurskal-Wallis Test; P<0.05, (c) Fisher exact Test; P<0.05, (d) Chi square test, P<0.05.
In both SCA2 and SCA3 groups, no correlation was found between muscle cramps frequency and disease duration (SCA2, $\rho = -.138$, $P = .583$; SCA3, $\rho = .129$, $P = .621$), frequency and muscle cramps duration (SCA2, $\rho = .297$, $P = .348$; SCA3, $\rho = .113$, $P = .725$) and quantity of muscle groups affected and SARA score (SCA2, $\rho = -.214$, $P = .424$; SCA3, $\rho = -.093$, $P = .729$).

Some studies have reported the prevalence of muscle cramps in SCA2, ranging from 6 to 81%.[5,6] In our study, 100% of the SCA2 patients presented cramps. Also, it was found that muscle cramps tend to occur 8 years earlier in SCA2 compared to SCA3, and neck and abdomen cramps were characteristic of SCA2 patients. Our study is in accordance with previous studies, that described the beginning of the muscle cramps in SCA2, occurring 4 to 6.5 years before the ataxia’s onset.[4,5] In addition to being an early symptom in SCA2, cramps progress in frequency, duration and amount of muscles involved, as the disease progresses.[6]

On the other hand, in SCA3 patients muscle cramps are more intense early in the disease course and tend to decrease severity as the muscular atrophy advances.[5] In the present study, SCA3 muscle cramps affected primarily lower and upper limbs, in accordance with the literature.[5] The correlation with greater tendency to statistical significance was the one between VAS and muscle cramp duration. In our study, we did not find any correlation between frequency, duration and quantity of muscles groups involved with disease duration. We did note, however, that muscle cramps occurred predominantly during nighttime and affected predominantly different muscle groups in SCA2 and SCA3 patients. Previous research involving patients with SCA3 showed a frequency of muscle cramps of about 80%,[5] a value similar to the one found in the present study. In SCA3, muscle cramps have been correlated to inferior motor neuron alterations, such as denervation and reinnervation recorded by electromyography.[5] The main factor that determines when muscle cramps will occur is the size of CAG triplet repetition.[6]

In conclusion, the present study found significant difference in muscle cramp frequency among SCAs, with high values in SCA2 and SCA3, being more frequent and presenting earlier in the first group. Muscle cramps arose before the ataxia in patients with SCA2 and SCA1, meanwhile patients with SCA3 showed after disease onset. These findings might allow a different approach during clinical investigation, although larger longitudinal studies are necessary to corroborate our findings.

## Table 2: Number of patients with muscle cramps per SCA type

| SCA2 | SCA3 | SCA10 | Others | P    |
|------|------|-------|--------|------|
| 18 (100%) | 17 (70.8%) | 5 (26.3%) | 4 (57%) | <0.0001^1 |
| 18 (100%) | 17 (70.8%) | - | - | 0.0140 |
| 18 (100%) | - | 5 (26.3%) | - | <0.0001^1 |
| 18 (100%) | - | - | 4 (57%) | 0.0152 |
| - | 17 (70.8%) | 5 (26.3%) | - | 0.0058^2 |
| - | 17 (70.8%) | - | 4 (57%) | 0.6518^3 |
| - | - | 5 (26.3%) | 4 (57%) | 0.1881^4 |

(a) Chi square test, $P<0.05$, (b) Fisher exact Test; $P>0.05$

## Ethics approval
We confirm that we have read the journal’s position on issues involved in ethical validation and affirm that this work is consistent with those guidelines.

## Declaration of patient consent
All patients included in this study gave written informed consent for the storage of their clinical data for research purposes.

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## Conflicts of interest
There are no conflicts of interest.

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