DR. CARLOS HENRIQUE FERREIRA CAMARGO (Orcid ID : 0000-0002-3533-0347)

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Balance and physical functioning in Spinocerebellar ataxias 3 and 10

Running tittle – Physical functioning in SCAs

Katia M. Konno, PT[1] katiakonno@gmail.com

Marise Bueno Zonta, PT, PhD[1,2] marisebzonta@gmail.com

Ana T.B. Guimarães, BSc, PhD[3] anatbguimares@gmail.com

Carlos Henrique F. Camargo, MD, PhD [2] chcamargo@uol.com.br

Renato Puppi Munhoz, MD, PhD[4] renatopuppi@gmail.com

Salmo Raskin, MD, PhD[5] genetika@genetika.com.br

Tetsuo Ashizawa, MD,[6] tashizawa@houstonmethodist.org

Helio A.G. Teive, MD, PhD[1,2] hagteive@mps.com.br

1- Movement Disorders Unit, Neurology Service, Internal Medicine Department, Hospital de Clínicas, Curitiba, Paraná, Brazil
2- Neurological Diseases Group, Graduate Program in Internal Medicine, Internal Medicine Department, Hospital de Clínicas, Federal University of Paraná, Curitiba, Paraná, Brazil
3- Center for Biological and Health Sciences - State University of Western Paraná, Cascavel, Paraná, Brazil

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4- Gloria and Morton Shulman Movement Disorders Centre, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada
5- Genetika - Centro de Aconselhamento e Laboratório de Genética, Curitiba, Paraná, Brazil
6- Neuroscience Research Program, Houston Methodist Neurological Institute and Research Institute, Weill Cornell Medical College, Houston, Texas, USA.

Corresponding Author: Carlos Henrique F Camargo. E-mail: chcamargo@uol.com.br Adress: Postgraduate Program in Internal Medicine, Hospital de Clínicas,Rua General Carneiro 181, Centro, Curitiba, PR, 80060-900, Brazil

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ABSTRACT

Objectives: Limitations of functional capacity and balance are common features of the natural history of spinocerebellar ataxias (SCA). However, their onset and progression patterns differ according to subtype. The aim of our study was to compare physical functionality and balance parameters in SCA10 and SCA3 patients, correlating with clinical variables. **Material & Methods:** Cross-sectional study evaluating ninety-five SCA patients (60 with SCA3 and 35 with SCA10) with validated scales for functional independence, balance and the severity of signs and symptoms. **Results:** The groups were similar in terms of age and gender, and results were adjusted for age at symptom onset. The SCA10 patients had better results for balance and functional independence ($p<0.007$). They also had lower scores for disease severity ($p<0.0002$) and the subitems gait ($p<0.0005$), posture ($p<0.0021$) and sitting balance ($p<0.0008$). Symptom progression in both groups was similar for patients with a disease duration of up to ten years, but there was a more marked decline in SCA3 patients after this period. **Conclusion:** We have shown that disease progression as assessed by balance and physical functioning is slower in SCA10 patients than SCA3 patients, particularly after 10 years of disease. These findings are important as they can help to characterize the disease, assisting in the development of new therapies and rehabilitation programs.

Keywords: Spinocerebellar ataxia; SCA3; SCA10; motor functionality; balance.

INTRODUCTION

The spinocerebellar ataxias (SCAs) represent a group of neurodegenerative diseases that affect balance and coordination with progressive limitation in functionality and eventual loss of independence [1-3]. The rate and array of symptoms progression in SCAs varies significantly according to several variables but primarily depend on disease subtype [4]. SCA type 3 (SCA3) is the most common and widely studied SCA [3,4]. From a clinical standpoint, this SCA subtype presents a wide range of phenotypes, including not only the cerebellar syndrome but also a wide range of ocular findings, pyramidal signs, other movement disorders (dystonia and parkinsonism) as well as peripheral neuropathy [5]. SCA10 is overall less common than SCA3 [6]. The condition is characterized clinically by cerebellar ataxia very often combined with epilepsy, and, less frequently, peripheral neuropathy, pyramidal signs and cognitive dysfunction [7]. Interestingly, a pure cerebellar form has been consistently described in South Brazil, with a prevalence of epilepsy much lower than reported elsewhere [8].

Unfortunately, these forms of SCA are currently managed with symptomatic treatment, while the neurodegenerative process per se is relentless [9]. Given the variable pattern of disease progression seen in these neurodegenerative diseases, the use of instruments that can assess the main clinical and functional landmarks of the advancing disease becomes of pivotal importance as potential longitudinal biomarkers [10,11]. Scale for the Assessment and Rating of Ataxia (SARA) [12] and Berg Balance Scale (BBS) [13] are identified as the best outcome measures for assessing balance in patients with cerebellar ataxia [14]. Both scales are highly correlated in ataxias because they measure the progression of cerebellar symptoms. Measures of balance can be categorized as static, dynamic, and specific cerebellar components [14]. The BBS is a generic instrument able to evaluate these three categories [13]. SARA is a measure of cerebellar function and three of its eight items address balance [12]. The combination of the two scales allows, besides a wider evaluation of balance, to capture a wide spectrum of balance functions.

Using specific parameters, the aim of this study was (1) to compare established parameters of balance and physical functionality in patients with SCA3 and SCA10; and (2) to correlate the severity of these same parameters with disease duration in each SCA type.

METHODS

A total of 117 patients, 68 with SCA3 and 39 with SCA10, were selected prospectively at the Ataxia Outpatient Clinic, Hospital de Clinicas, Federal University of Paraná between January 2013 and May 2016. Twelve were excluded, and 95 patients with genetically proven diagnoses of SCA10 (n=35) and SCA3 (n=60) were recruited. The study was approved by the Committee for Ethics in Human Research at the Hospital de Clínicas (CAAE 18722413.9.0000.0096, ref. 430.527), and all the participants signed a voluntary consent form in accordance with the guidelines in National Health Council (CNS) Resolution no. 186/96.

Patients were included if they were older than 18 years old, had a clinical and genetically confirmed diagnosis of SCA3 or SCA10 and were able to understand and sign the consent to participate. SCA10 was confirmed by detection of an expansion with more than 800 ATTCT pentanucleotide repeats in the *ATXN10* gene on chromosome 22q13, and SCA3 was confirmed by the presence of a CAG trinucleotide repeat expansion with more than 51 repeats in the *ATXN3* gene on chromosome 14q24.3-q31. Patients with concomitant neurological diseases were also excluded, as were patients with other conditions such as alcoholism and systemic malignant neoplasms or with spasticity and dystonia lower limbs or who were using medications with potentially adverse effects that could interfere with the test results (e.g, phenytoin, anti-spastic or anticholinergic agents).

All were assessed through a standardized protocol in which the following variables were collected: demographic data, details of clinical history, physical examination, functional, and balance assessment. Balance was assessed using the Brazilian Portuguese version of the Berg Balance Scale (BBS) [13], which assesses static and dynamic balance. The tasks used are assessed by observation using a score of 0 to 4 to each task, summing up a maximum of 56 points. The score is based on the time for which the position can be maintained, how far forward the individual can extend the arm and the time taken to complete a task. Lower scores indicate worse performances. The cut off for balance is 46. Scores below 46 indicate compromise of balance and an increased risk for falls.

Functional assessment used the Brazilian Portuguese versions of the Functional Independence Measure (FIM) [15] and Lawton scale [16]. Both are used to evaluate

independence in activities of daily living (ADLs) and instrumental activities of daily living (IADLs) as well as social cognition. To adapt the Lawton scale for the different activities typically carried out by males and females, the question about housekeeping tasks was replaced by a question about minor repairs in the house or caring for the garden. For both scales, higher scores denote a greater level of independence. In addition, signs of ataxia were rated using Portuguese version of the Scale for the Assessment and Rating of Ataxia (SARA) [12]. The SARA has eight items addressing gait, posture, balance, alterations in speech, coordination and diadochokinesia. The total ranges from 0 (without ataxia) to 40 (most severe form of ataxia) [12].

Finally, to compare these clinical parameters over the time course of both forms of SCA, we compared them also based on disease duration using an arbitrary period of 10 years intervals: less than 10 years, 10 to 20 years, and more than 20 years of disease duration. The age at onset of symptoms was recorded according to patient's report and was defined as the age at which the patient first detected gait ataxia. For some of the analyses, the SCA3 and SCA10 groups were adjusted by gender, age, age at symptoms onset, and disease duration.

Statistical analysis was performed using with R statistical software. Continuous variables were tested for normality with the Shapiro-Wilk and Shapiro-Francia tests. Kruskal-Wallis test was used for multiple comparison analysis. Means and medians were compared with Student's t test and the Wilcoxon-Mann-Whitney test, respectively. Spearman's correlation coefficients were estimated to determine the association between two quantitative variables. A significance level of $p < 0.05$ was used.

RESULTS

Patients were grouped according to the molecular diagnosis. Differences for gender proportion and age were not statistically different between both groups as shown in Table 1. This table also shows mean size of ATTCT and CAG repeats expansion.

Although patients with SCA10 had a longer duration of disease ($p = 0.004$), mean balance scores, as measured by the BBS, were statistically higher (better) for SCA10 patients than for the SCA3 patients ($p= 0.007$), in both cases presenting worsening of scores at every bracket of disease duration, as shown in Table 1 and 3. After adjustment

for disease duration, there were statistical differences for all the evaluation parameters used (Table 1).

Although the mean BBS score for both groups were below the established cutoff, the percentage of cases at risk for falls was significantly higher among SCA3 patients (65% vs. 40%, p=0.0204). While average score for balance in the SCA10 group was 44.6 ±10.8, indicating a moderate risk for falls, the figure for the SCA3 patients was 36.6 ±15.5, indicating high risk for recurrent falls over 6 months follow up. Functional independence, which is broken down into motor (p<0.0007) and cognitive scores (p<0.0205), was significantly higher in the SCA10 group, indicating greater independence in ADLs. These patients also had a better mean score for IADLs (p<0.007) than patients in the SCA3 group (Table 1).

Similarly, mean SARA scores differed significantly between the two groups (p<0.0002), showing lower severity in the SCA10 group. Among the eight subitems of this scale, the ones that assess appendicular signs (heel-to-chin, finger chase, alternating hand movements, and nose-finger tests) had scores that did not differ significantly between groups as opposed to the ones that assess axial (posture, speech and sitting) and gait ataxia as shown in Table 2.

To assess the symptoms, signs and functionality decline over the course of the disease, we compared the mean scores of the variables for each disease duration bracket. In both groups were similar for patients with a disease duration of up to ten years. Mean FIM score was 118.6 (n=19) for the SCA10 group and 110.7 (n=39) for the SCA3 group (Table 3). After ten years, however, symptom progression was different in the two groups, a more pronounced decline being observed in the SCA3 group. Although the scales revealed moderate dependence in patients in both groups, the SCA10 group (p=0.0117) had significantly higher FIM scores (p=0.0002) considering disease duration (Table 3).

There was a correlation between BBS and the scales that measured ADLs in patients with SCA3 and SCA10, but there was no correlation between these scales and SARA in patients with SCA3 (Table 4).

DISCUSSION

The findings of this comparative study of SCA3 and SCA10 patients show that disease severity and the decline in balance and functional independence progressed at similar rates in both groups during the first ten years and that the decline accelerated significantly in SCA3 patients after this. We acknowledge the caveat that the study had a cross-sectional design, and patients were divided into age strata. Therefore, our study did not follow the patients longitudinally for more than 20 years. As such, we recommend the reader to interpret the results in light of these limitations.

In SCAs, in general, the correlation between disease severity and disease duration has been described [17], as well as the correlation between greater functional loss and higher SARA scores [10,18]. It is well established that, due to the progressive course of the disease, impaired motor coordination and balance inevitably lead to loss of independence. The present study gives us a better understanding of the differences in progression of functional loss in two different types of SCAs and may better characterize the loss in SCA10. With these results, it is possible to better plan the management of these patients by differentiating treatment and rehabilitation approaches focused on SCA3 and SCA10 patients.

The differences observed between the groups in the items gait, sitting balance and posture on the SARA scale, which can be used to distinguish the different patterns of progression, can be explained by the more rapidly progressing impairment of the lower limbs in SCA3 patients [19-24]. Another factor that may account for the worse scores in SCA3 is the higher frequency of peripheral nervous system impairment in this form of the disease, which is determined primarily by disease duration and therefore found more frequently in patients who have had the disease for longer [10]. The incidence of peripheral neuropathy in SCA3 was described by Coutinho as 60% [25].

The balance in patients with SCA10 was significantly better than in those with SCA3 and was not associated with disease duration in either group, corroborating the study by Aizawa et al. [1]. In a study of 44 individuals with different types of SCA (4 with SCA1, 12 with SCA2, 21 with SCA3 and 9 with SCA6), Aizawa et al.[1] found that balance varied with the type of ataxia and that disease severity and balance were associated with a greater loss of physical functioning (self-care, transfers and locomotion) but failed to find an association with disease duration.

In the present study, increased loss of balance was associated with greater disease severity, greater functional loss, and a higher risk of falls in both groups, with a slower evolution in SCA10. The balance and functional scales scores in SCA10 remain more stable and the disease progresses more slowly, especially after 10 years of disease. The less aggressive anatomical and pathological features of SCA10 may be one of the factors that contribute to a more favorable progression in this form of the disease [26,27]. Another explanation for this finding is the fact that in Brazil SCA10 presents in the pure cerebellar form, where functional loss would be slower [28].

Balance for walking and motor coordination are prerequisites for independence in ADLs [1,2]. The scores for both groups in this study indicate that the patients had reduced independence in both AIVDs and ADLs, i.e., and required help from others to perform certain tasks. The SCA10 patients, however, retained their independence for longer. Although reduced independence is common to both forms of SCA studied here, it progresses more slowly in SCA10 patients.

This was also observed for the activities analyzed social cognition in the FIM subscale. In our study, this subscale, which assesses the ability to identify and adjust behavior to the individual's environment, showed that SCA10 patients had better scores for the items problem solving, social interaction, comprehension and expression. As the instrumental tasks demanded higher cognition [29], greater difficulty could be expected in individuals with SCA10. Although patients with cerebellar dysfunction are known to present with Schmahmann's syndrome, which includes executive dysfunction, spatial dysfunction, language deficits (phonemic fluency) and personality disorders as prime examples of cognitive impairment [30], cognitive decline in SCAs varies and is not correlated with cerebellar atrophy [31].

In conclusion, our findings indicate that balance, functional independence for ADLs and IADLs and disease severity scores tend to be less severe in SCA10 compared to SCA3. Although similar during the first ten years, the scores were worse in SCA3 after this. SCA10 progression is slower, and this could be observed particularly in the subitems assessing balance. These findings are important as they can help to characterize the disease, assisting in the development of new therapies and rehabilitation programs. However, further studies with a larger population sample are required to confirm them.

Declaration of Conflicting Interests

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Authors' Roles

Katia Mayumi Konno: contributed to the study design, data acquisition, statistical analysis, data interpretation and drafting of the manuscript.

Marise Bueno Zonta: contributed to the study design, data analysis, data interpretation and preparation and critical review of the manuscript.

Ana Tereza Bittencourt Guimarães: contributed to the statistical analysis and interpretation of the results.

Carlos Henrique F. Camargo: contributed to the statistical analysis, interpretation of the results and critical review of the manuscript.

Renato Puppi Munhoz: contributed to the interpretation of the results and preparation and critical review of the manuscript.

Salmo Raskin: contributed to the study design and conducted the genetic tests.

Tetsuo Ashizawa: contributed to the study design and conducted the genetic tests.

Hélio Afonso Ghizoni Teive: contributed to the study design, evaluation of the data and critical review of the manuscript.

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TABLES

Table 1. Study sample data and scores.

	Without adjustment (disease duration)			With adjustment (disease duration)		
	SCA3 (n=60)	SCA10 (n=35)	p value*	SCA3 (n=44)	SCA10 (n=31)	p value*
Age	43.76±12.28	45.46±9.46	0.117	48.47±12.53	46.96±9.43	0.286
Age at onset of symptoms	34.76±10.75	33.86±8.3	0.462	35.02±10.34	35.41±8.75	0.431
Disease duration	9.16±5.6	11.57±7.52	0.004	13.45±4.49	11.54±7.46	0.086
Genetic data (no. of ATTCT and CAG repeats)	64.8±14.9	1960.8±304.2	NA	66.91±13.96	1936.8±246.2	NA
SARA	14.33±7.3	8.83±5.5	0.0002	19.13±7.14	11.38±6.96	<0.0001
Berg balance score	36.10±15.5	44.6±10.8	0.007	27.63±16.05	44.67±12.81	<0.0001
Lawton IADL score	17.1±4.2	18.86±3.2	0.032	15.77±3.87	18.29±3.41	0.0005
FIM total score	104.6±16.5	115.8±9.2	0.001	98.15±18.13	110.77±11.35	0.0023

SARA: Scale for the Assessment and Rating of Ataxia; SCA10: spinocerebellar ataxia type 10; SCA3 spinocerebellar ataxia type 3; SD: standard deviation; FIM: Functional Independence Measure; NA: not applicable; *statistical significance was set at p<0.05, Student's t.

SARA – 0 to 40 – higher scores = worse cerebellar symptoms

BBS – 0 to 56 – lower scores = poorer balance

Lawton and FIM – higher scores = greater level of independence

Table 2. Comparison of disease severity (SARA) for the SCA3 and SCA10 groups.

Variables (items of SARA)	**SCA3 (n=60)**	**SCA10 (n=35)**	**p***
Gait	3.73±2.1	2.23±1.6	0.0005
Posture	2.58±1.9	1.37±1.3	0.0029
Sitting balance	1.02±1.3	0.23±0.5	0.0008
Speech disturbance	2.17±1.3	1.4±1	0.0126
Finger-chase test	1.18±0.8	0.91±0.7	0.1252
Nose-finger test	0.8±0.9	0.51±0.7	0.1226
Rapid alternating hand movements	1.35±1	0.94±0.9	0.0505
Heel-to-shin test	1.61±1	1.31±0.8	0.1828
Total	**14.33±7.3**	**8.83±5.5**	**0.0002**

SARA: Scale for the Assessment and Rating of Ataxia; SCA10: spinocerebellar ataxia type 10; SCA3 spinocerebellar ataxia type 3; SD: standard deviation; *statistical significance was set at p<.05, Student's t and Wilcoxon-Mann-Whitney tests

SARA – 0 to 40 – higher scores = worse cerebellar symptoms

Table 3. Comparison of SCA3 and SCA10 scores: subgroups of patients by disease duration

Type of SCA	Time since onset of symptoms	N	Disease duration (years)	SARA	FIM	BBS	LAWTON
SCA3	< 10 years	39	9.32±0.47	12 (0-26)	112 (68-126)	45 (4-56)	20 (7-21)
	10 to 20 years	19	17.25±1.69	19 (5-29)	90 (72-125)	26 (4-56)	16 (9-21)
	> 20 years	2	24.5±0.70	27 (21-33)	69.5 (67-72)	13.5 (6-21)	8.5 (7-10)
	p value			0.0001	0.0002	0.003	0.015
SCA10	< 10 years	19	6±3.09	7 (1-16)	122 (92-125)	52 (31-56)	21 (16-21)
	10 to 20 years	13	15.92±3.22	9 (3-26)	117 (102-125)	43 (13-55)	20 (12-21)
	> 20 years	3	31.9±8.0	16 10-19)	100 (88-111)	27 (21-32)	11 (10-17)
	p value			0.0236	0.0117	0.007	0.0022

SCA10: spinocerebellar ataxia type 10; SCA3 spinocerebellar ataxia type 3; SARA: Scale for the Assessment and Rating of Ataxia; FIM Functional Independence Measure; BBS Berg balance scale *statistical significance was set at p<.05, Kruskal-Wallis test.

SARA – 0 to 40 – higher scores = worse cerebellar symptoms
BBS – 0 to 56 – lower scores = poorer balance
Lawton and FIM – higher scores = greater level of independence

Table 4. Comparison of SCA3 and SCA10 correlation scores

	SCA3	**SCA10**
SARA x LAWTON	r_s = -0.217, p = 0.184	r_s = -0.494, p = 0.004
SARA x FIM	r_s = -0.151, p = 0.355	r_s = -0.473, p = 0.006
BBS x LAWTON	r_s = 0.612, p < 0.0001	r_s = 0.609, p = 0.0002
BBS X FIM	r_s = 0.418, p = 0.008	r_s = 0.534, p = 0.001

SARA: Scale for the Assessment and Rating of Ataxia; FIM Functional Independence Measure; BBS Berg balance scale *statistical significance was set at p<.05, Spearman correlation test.