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Spinocerebellar ataxias in Southern Brazil: Genotypic and phenotypic evaluation of 213 families

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ABSTRACT

Objectives: To describe and correlate the genotype and phenotype of patients diagnosed with SCAs in southern of Brazil.
Patients and methods: Data were collected from the records of our ataxia outpatient clinic. We included 460 patients from 213 families, who were divided into four groups: SCA3, SCA10, Other SCAs and Undetermined.
Results: The most frequent type was SCA3 (45.7%), followed by SCA10 (18.3%), SCA2 (6.5%), SCA1 (4.3%), SCA7 (1.8%), and SCA6 (0.65%). The Undetermined group represented 22.8% of all patients. We observed a high frequency of SCA10 when compared to data from other studies, which can be explained by a founder effect in our region. Statistically significant differences were found for several symptoms when comparing SCA groups, especially lid retraction ($p < 0.001$), ophthalmoplegia ($p < 0.001$), visual loss ($p < 0.001$) and slow saccades ($p < 0.001$) which may help clinically differentiate SCAs and allow neurologists to request the right confirmatory genetic test and define prognosis. Also, the prevalence of epilepsy in SCA10 patients was lower than usual (4.8%), suggesting a genetic variation of the disease.
Conclusion: Although SCA3 remains the most common, we observed a high frequency of SCA10 in our region. In addition, some symptoms and signs might help differentiate the SCAs.

1. Introduction

Spinocerebellar ataxias (SCAs) are a group of rare autosomal dominant neurodegenerative disorders, genetically and clinically heterogeneous, characterized by progressive cerebellar dysfunction (mainly gait and limb ataxia) variably associated with extracerebellar signs such as ophthalmoplegia, Parkinsonism, cognitive impairment, epilepsy, and peripheral neuropathy [1]. There are many different types of SCAs, and they are classified based on the gene mutation responsible for the particular SCA type. There are at least 48 genetic loci that have been associated with SCAs [2,3]. The most common mutations described are secondary to trinucleotide repetition expansions [4,5].

The frequency of each type of SCA varies according to geographic region and ancestry. It is known that the most common of all ataxias is the Machado-Joseph disease (SCA3), followed by SCA2, SCA1 and SCA6 [1,2,6,7]. In Brazil, the epidemiological studies of SCAs were conducted in the South and Southeast [8–10], confirming the higher occurrence of SCA3 and SCA10. SCA3 is caused by mutations in the *ATXN3* gene. When mutated, this gene has increased number of CAG repeats, usually greater than 60 repeats [4]. SCA3 is associated with a myriad of symptoms including cerebellar ataxia, pyramidal, peripheral neuropathy, movement disorders, and oculomotor findings [4]. SCA10 was diagnosed initially in Mexico and in South American countries such as Brazil, Argentina, Venezuela, and Peru [11–17]. Recently, the first cases

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of SCA10 were observed in the East, more specifically in China and Japan [18,19]. SCA10 is an almost pure type of SCA in some areas characterized by slowly progressive cerebellar ataxia, dysarthria, dysphagia, and cognitive symptoms. Epilepsy is an important finding of this SCA and it can be found variably, e.g., 3.5% in families from specific states in Brazil (Parana and Santa Catarina) whereas this figure was found to be 64.7% in families from other Brazilian states [13,14,17,20]. SCA10 is caused by expansion of ATTCT pentanucleotide repeats in the *ATXN10* gene [12–15].

In 2012, our group studied 150 patients from 104 families with SCAs, which had been extracted from a large Brazilian series of 190 SCA families, recruited between 1989 and 2009. Mutations were identified in 66.3% of the families and were most frequently identified for SCA3 (72.46%). SCA10 represented the second most common type of SCA (11.60%), followed by SCA2 (7.25%), SCA7 (4.34%), SCA1 (2.90%), and SCA6 (1.45%) [8]. In this study, we aim to expand the epidemiological and genotypic/phenotypic knowledge in SCA families from Southern Brazil.

2. Patients and methods

2.1. Selection of patients

We reviewed charts of patients with SCAs who were being followed at the Ataxia Outpatient Clinic of Movement Disorders Unit at the Hospital de Clínicas, from Federal University of Parana, from February 2012 to February 2017. We selected 460 patients, from 213 families from Southern Brazil, diagnosed with SCAs. Some of these patients were also being followed up between 1989 and 2009, including in the study performed by Teive et al. [8]. Patients had: (1) clinical and genetic diagnosis, or (2) clinical features and relatives with genetic confirmation (3) clinical diagnosis and family with autosomal dominant inheritance, but no genetic evaluation was completed. Incomplete charts at level of being impossible to confirm an autosomal dominant SCA were excluded. Due to the small number of patients with some types of SCAs (SCA1, SCA2, SCA6, SCA7), for some analyzes they were gathered in a group called "Other Ataxias". Another group was formed with patients without genetic confirmation (negative for the most common types of SCAs [47 patients] or untested [58 patients]), called "Undetermined". HC-UFPR ethics committee approved this study.

2.2. Clinical and genetic data collection

Clinical and demographic variables (address, origin, ethnicity of parents and grandparents, sex, age, age at onset of disease, duration of disease, main symptoms and comorbidities) were collected by means of a standardized semi-structured questionnaire. A subset of patients had been scored for the severity of their ataxia according to the Scale for the Assessment and Rating of Ataxia (SARA), which ranged from a total score of 0 (no ataxia) to 40 (most severe ataxia) [21]. The screening test for cognition deficits applied was the Mini Mental State Exam (MMSE), using the cutoffs for dementia adapted for Brazilian culture for Bertolucci et al. [22]. Genetic assessments were done, in the same or in partner institutions, for previous studies of SCAs [8,13,15,20]. SCAs 1, 2, 3, 6, 7 and 10 were tested. Results from genetic analyzes were also collected from the charts.

The researchers were not blinded to genetic results when they were collecting epidemiological and clinical data.

2.3. Statistics

Results were presented as means, medians, minimum and maximum values, and standard deviations (quantitative variables) or as frequencies and percentages (categorical variables). ANOVA with one factor or the non-parametric Kruskal-Wallis test were used to compare the four groups in terms of quantitative variables. LSD test (least significant difference) was used for multiple comparisons within the groups (post-hoc). The normality of the variables was evaluated by the Kolmogorov-Smirnov test. For the comparison of the groups in relation to categorical variables, the Chi-square test was used. To evaluate the association between two quantitative variables, the Pearson or Spearman correlation coefficient was estimated, depending on the normality of the variables. Values of $p < 0.05$ indicated statistical significance. Data were analyzed using the IBM SPSS Statistics v.20.0 software.

3. Results

Among the 460 patients, 355 (77.2%) had their diagnosis confirmed by genetic testing (index case or of close relative). These patients were divided into four different groups: SCA3 (n = 210, 45.7%), SCA10 (n = 84, 18.3%), Other SCAs (n = 61, 13.3%) and Undetermined (n = 105, 22.8%). The Other SCAs group was composed by 20 (32.8%) cases of SCA1, 30 (49.2%) of SCA2, 3 (4.9%) of SCA6 and 8 (13.1%) of SCA7.

There were no differences regarding gender, age at onset of the disease and disease duration between these four groups. Despite the similarity in mean disease duration between groups, patients with SCA10 presented lower disease severity, with lower SARA scores ($p = 0.029$) (Table 1).

There was correlation among SCAs severity by SARA and disease duration for SCA3 (rho = 0.27, $p = 0.046$), SCA10 (rho = 0.39, $p = 0.031$) and Other SCAs (rho = 0.45, $p = 0.007$) (Table 2). The age of onset for the SCA3 (rho = −0.47, $p < 0.001$) and SCA10 (rho = −0.35, $p = 0.021$) groups was inversely correlated with the number of expansions, i.e., early onset patients may have larger mutated sequences (Table 2).

Dysarthria and gait ataxia are common symptoms in patients with SCAs (Table 3). However, we observed that several of the symptoms raised had a very significant statistical difference between groups. Among them, we highlight the presence of lid retraction ($p < 0.001$) in 57.6% of SCA3; slow saccadic eye movement ($p < 0.001$) in 83.4% of SCA2; visual loss ($p < 0.001$) in 100% of SCA7; Parkinsonism only in SCA3 patients; fasciculation ($p < 0.001$) in 11.9% of SCA3. In relation to epilepsy, we found very low frequencies in all groups, including the SCA10 group (4.8%) (Table 3).

We collected the individuals' origins. Of all the cities listed, the largest group came from Itajaí, coast of Santa Catarina (n = 90). Of these, the majority (n = 61) corresponded to the SCA3, followed by SCA10 (n = 24). The second most represented city was Curitiba, Parana, with 88 individuals. We observed that a large part of these patients also had their family origin traced back to the coast of Santa Catarina. All cases of SCA10 analyzed in the present study originated in Parana or Santa Catarina (Table 1). As for ethnicities, the majority of patients with SCA3 were Portuguese descendants (mainly Azorean). The Portuguese, German and Belgian SCA10 families assimilated native Indians in their pedigrees. Patients with SCA6 were Japanese, and patients with other SCAs had European ancestry (Table 1).

Clinical, demographic, and genetic data were not available for all patients because they were not obtained or properly noted in the medical records.

4. Discussion

SCA3 was the most frequent SCA observed in our study. SCA3 is the most common type worldwide, representing 21% of all SCAs [2]. It is the most common SCA in Brazil (30–92%) [8–10,23,24], and in other American countries such as the USA (33.9%) [25] and Canada (23.8%) [26]. SCA10 was in second place in our sample, despite its rarity worldwide [2,27]. These data can be explained by a founder effect in

Table 1
SCAs clinical, epidemiological and genetic indicators.

Variable	SCA3 (n = 210)	SCA10 (n = 84)	Other SCAs (n = 61)	Undetermined (n = 105)	p value*
Gender - male (%)	52.9 (111)	46.4 (39)	57.4 (35)	48.6 (51)	0.529**
Age - years	44.1 ± 12.1 (208)	45.5 ± 11.5 (82)	41.6 ± 13.1 (60)	42.3 ± 13.0 (104)	0.171
Age at onset - years	35.3 ± 9.4 (207)	35.2 ± 9.5 (82)	32.7 ± 11.0 (60)	33.1 ± 11.5 (100)	0.137
Disease duration -years	8.8 ± 6.9 (207)	10.4 ± 8.9 (82)	9.0 ± 6.7 (60)	9.1 ± 7.5 (100)	0.874
Expansion -mutated gene	70.8 ± 5.3 (120)	1874 ± 422 (44)	SCA1 – 48.9 ± 5.9 (10) SCA2 – 45.2 ± 2.8 (13) SCA6 – 24 (2) SCA7 – 64.8 ± 2 (5)	NA	NA
SARA	17.1 ± 12.0 (59)	11.3 ± 6.2 (32)	16.6 ± 9.0 (34)	14.2 ± 9.0 (51)	0.029
Origin#	MRC – 36 (17.2) PSI – 14 (6.7) CSC – 114 (54.3) OL – 24 (11.40) UK – 22 (10.5)	MRC – 18 (21.4) PSI – 0 (0) CSC – 62 (73.8) OL – 0 (0) UK – 5 (5.9)+	MRC – 43 (70.5) PSI – 7 (11.5) CSC – 3 (4.9) OL – 3 (4.9) UK – 5 (8.2)	MRC – 52 (49.5) PSI – 17 (16.2) CSC – 15 (14.4) OL – 10 (9.5) UK – 13 (12.4)	< 0.001***
Main Ethnicity	Portuguese (Azorean), German and Spanish	Native Indian (with Portuguese, German and Belgian families)	SCA1 – Italian SCA2 – Spanish SCA6 – Japanese SCA7 - Portuguese	Portuguese, Italian, Spanish, German and Native Indian	NA

SARA: Scale for the assessment and rating of ataxia; SCA: Spinocerebellar ataxia; NA: not applicable.

* Comparison between 4 groups (ANOVA with one factor for current age and onset age; non-parametric Kruskal-Wallis test for disease duration, expansion and SARA; $p < 005$).

** Comparison between 4 groups (chi-square test; $p < 005$).

*** State of Parana X State of Santa Catarina (chi-square test; $p < 005$).

Origin – MRC: Metropolitan Region of Curitiba (PR); PSI: Parana State Interior; CSC: Coast of Santa Catarina; OL: Other Localities; UK – Unknown ancestry.

\+ Patients with families from Santa Catarina or Parana.

Latin America where most of the SCA10 cases appear to have a common descent, originating from an Amerindian ancestral population that spread through countries such as Mexico and Brazil [28,29]. Other studies also point out that in our country, families with this SCA originated from the coastal region of the Santa Catarina, between São Francisco do Sul and Florianópolis, as well as from the Itajaí Valley, in the city of Ilhota [30], which justifies the great amount of cases originated from these regions. Due to colonization by the Azoreans, most of our SCA3 patients also originated from this region of Santa Catarina. Except SCA3 and SCA10, other SCA patients were predominantly from the state of Parana. This state received little Azorean immigration and a greater Italian, Spanish, Japanese and Slavic colonization than Santa Catarina. The three patients with SCA6 were Japanese descendants from Parana.

Our decision to request tests for an index case of each family could be justified by the important hereditary factor involved in the development of the SCAs. However, the real reason for this decision was the lack of funding for research, a common limiting factor in developing countries. Nevertheless, the percentage of patients with positive genetic testing was compatible with the literature [2,7–10]. Despite this, a large number of patients in this sample do not have a confirmed genetic diagnosis of SCA, an important limitation of the study. The Undetermined group may contain patients with both rare and common types of SCAs.

The analysis of the categorical variables brought very relevant findings. We emphasize the importance of clinical observation for the definition of the SCAs type as well as the specific genetic test to be performed. In our study, we found a series of symptoms such as lid retraction, horizontal ophthalmoplegia, vertical ophthalmoplegia, Parkinsonism, pyramidal signs and fasciculation, all of which are more prevalent in SCA3. Slow saccadic eye movements and hypo/areflexia were more common in SCA2, and visual loss in SCA7. SCA6 was almost pure SCA, but one case had dystonia, a rare finding in SCAs excluding SCA3. If observed carefully, the clinical symptoms can guide the neurologist to define the genetic test. Since genetic testing is not always possible at first, clinical guidance, made possible by significant differences in symptomatology between types of SCAs, may assist the physician when requesting varied types of tests, saving patients and institutions from unnecessary expenses. Also, this clinical suspicion may determine the prognosis of the disease, given the fact that SCA3 progresses with greater severity and speed [31] whereas SCA10 is characterized by a slower progression [14].

Another finding that makes this study stands out is the frequency of cases with epilepsy. It is known that this symptom is not very common among ataxias, except for SCA10, which is classically characterized by the association of cerebellar ataxia and epilepsy [12,14]. Curiously however, in our series of families, we recorded only 4 cases of epilepsy,

Table 2
Association between current age, age at onset, disease duration, expansion and SARA in the SCAs groups.

Variables	SCA3			SCA 10			Other SCAs		
	n	rho	p value	n	rho	p value	n	rho	p value
Current age x expansion	120	−0.40	< 0.001	44	−0.34	0.025	–	–	–
Current age x SARA	58	0.03	0.845	30	0.20	0.290	34	0.31	0.079
Age onset x expansion	120	−0.47	< 0.001	44	−0.35	0.021	–	–	–
Age onset x SARA	57	−0.08	0.554	30	−0.07	0.712	34	0.08	0.657
Disease duration x expansion	118	−0.08	0.417	44	−0.23	0.133	–	–	–
Disease duration x SARA	57	0.27	0.046	30	0.39	0.031	34	0.45	0.007

The Spearman correlation coefficient (rho) was estimated to evaluate the association between two quantitative variables. Values of $p < 005$ indicate a statistically significant correlation.

SARA: Scale for the assessment and rating of ataxia; SCA: Spinocerebellar ataxia.

Table 3
Main clinical findings in SCAs.

Variable	SCA3 (n = 210)	SCA10 (n = 84)	SCA2 (n = 30)	SCA1 (n = 20)	SCA7 (n = 8)	SCA6 (n = 3)	p value*
Gait ataxia	202 (96.2)	80 (95.2)	29 (96.7)	20 (100)	8 (100)	3 (100)	0.790
Dysarthria	187 (89.1)	79 (94.1)	25 (83.4)	18 (90)	8 (100)	3 (100)	0.480
Dysphagia	36 (17.1)	7 (8.3)	7 (23.4)	5 (25)	3 (37.5)	0 (0)	0.093
Nystagmus	190 (90.5)	73 (86.9)	4 (13.4)	9 (45)	4 (50)	3 (100)	< 0.001
Lid retraction	121 (57.6)	1 (1.2)	2 (6.7)	3 (15)	0 (0)	0 (0)	< 0.001
Slow saccades	16 (7.6)	5 (6)	25 (83.4)	5 (25)	2 (25)	1 (33.3)	< 0.001
Horizontal Ophthalmoplegia	142 (67.6)	8 (9.5)	5 (16.7)	1 (5)	1 (12.5)	0 (0)	< 0.001
Vertical Ophthalmoplegia	24 (23.5)	1 (1.3)	2 (6.7)	1 (5)	1 (12.5)	0 (0)	0.021
Visual loss	7 (3.3)	4 (4.8)	0 (0)	1 (5)	8 (100)	0 (0)	< 0.001
Parkinsonism	15 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.055
Tremor	5 (2.4)	5 (6)	3 (10)	2 (10)	0 (0)	0 (0)	0.221
Dystonia	15 (7.1)	0 (0)	0 (0)	0 (0)	1 (12.5)	1 (33.3)	0.007
Babinski sign	52 (24.8)	1 (1.2)	0 (0)	4 (20)	4 (50)	0 (0)	< 0.001
Hypo/Areflexia	26 (12.4)	2 (2.4)	20 (66.7)	1 (5)	0 (0)	0 (0)	< 0.001
Amyotrophy	24 (11.4)	0 (0)	4 (13.4)	1 (5)	0 (0)	0 (0)	0.025
Limb fasciculation	25 (11.9)	0 (0)	1 (3.4)	0 (0)	0 (0)	0 (0)	0.005
Facial fasciculation	59 (28.1)	1 (1.2)	1 (3.4)	1 (5)	0 (0)	0 (0)	< 0.001
Epilepsy	2 (1)	4 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0.260
Cognitive dysfunction	2 (1)	3 (3.6)	4 (13.4)	1 (5)	2 (25)	0 (0)	< 0.001
Neurogenic bladder	7 (3.3)	1 (1.2)	0 (0)	3 (15)	1 (12.5)	0 (0)	0.026

* Comparison between 6 groups (chi-square test; $p < 0.05$).

which allows us to state that our cases presented pure SCA, a rare phenomenon in other sites with high frequencies of SCA10 (Mexico, other regions of Brazil and other Latin American countries, including Peru) [10,29]. It is believed that the epileptic phenotype is related to the occurrence of interruptions in the ATTCT expansions of patients with SCA10, a hypothesis raised by Matsuura et al. [32] and corroborated by studies by McFarland et al. [33]. Future studies should be performed aiming to evaluate the occurrence of interruptions in the population of the present study, which may justify the low frequency of epilepsy observed.

The biggest limitation to our study was found during data collection, due to the lack of information such as symptoms or dates in some of the medical records. Despite the lack of data from many patients, an interesting finding was the relationship that we observed between the disease duration and the SARA (Scale for the Assessment and Rating of Ataxia) [34]. Reasonably, it is presumed that longer the evolution of ataxia, greater would be the symptomatology presented, given the deterioration of the patient would be progressive. Thus, our work reinforces this hypothesis for most cases with defined ataxia, that is, for the groups SCA3, SCA10 and Other SCAs. Similarly, we found an inverse relationship between the age of onset of symptoms and the expansions for SCA3 and SCA10, meaning, the lower the age of onset of the disease, the greater the expansions found in the genetic test. Data from the literature point to the existence of the genetic phenomenon of anticipation in both SCA3 and SCA10, which the increase in the number of pathological expansions is transmitted to the next generations causing an earlier onset of the disease and worse evolution in each subsequent generation [35,36]. The number of replicates of the mutated gene sequence can lead a higher toxicity and precocity in the cerebellar deterioration due to the accumulation of these proteins in the nervous tissue [35,37].

New research should therefore be done so that a deeper and more detailed analysis can be established, with precise values of the interaction between these variables. In addition, another aspect that should be better explored in future research is a greater diversity when it comes to the origin of cases. There is still no Brazilian or Latin American or American epidemiological complete panorama of SCAs, only specific groups of research in isolated regions. A greater integration among research groups and collaboration with international ones is direly needed.

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Declaration of Competing Interest
The authors declare no conflicts of interest with this study.

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