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Nonmotor Symptoms in Patients with Spinocerebellar Ataxia Type 10

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Abstract Nonmotor symptoms (NMS) have been described in several neurodegenerative diseases but have not been systematically evaluated in spinocerebellar ataxia type 10 (SCA10). The objective of the study is to compare the frequency of NMS in patients with SCA10, Machado-Joseph disease (MJD), and healthy controls. Twenty-eight SCA10, 28 MJD, and 28 healthy subjects were prospectively assessed using validated screening tools for chronic pain, autonomic symptoms, fatigue, sleep disturbances, psychiatric disorders, and cognitive function. Chronic pain was present with similar prevalence among SCA10 patients and healthy controls but was more frequent in MJD. Similarly, autonomic symptoms were found in SCA10 in the same proportion of healthy individuals, while the MJD group had higher frequencies. Restless legs syndrome and REM sleep behavior disorder were uncommon in SCA10. The mean scores of excessive daytime sleepiness were worse in the SCA10 group. Scores of fatigue were higher in the SCA10 sample compared to healthy individuals, but better than in the MJD. Psychiatric disorders were generally more prevalent in both spinocerebellar ataxias than among healthy controls. The cognitive performance of healthy controls was better compared with SCA10 patients and MJD, which showed the worst scores. Although NMS were present among SCA10 patients in a higher proportion compared to healthy controls, they were more frequent and severe in MJD. In spite of these comparisons, we were able to identify NMS with significant functional impact in patients with SCA10, indicating the need for their systematic screening aiming at optimal treatment and improvement in quality of life.

Keywords Spinocerebellar ataxia type 10 · Machado-Joseph disease · Nonmotor symptoms · Spinocerebellar ataxia type 3

Introduction

Spinocerebellar ataxia type 10 (SCA10) is a rare, dominantly inherited neurodegenerative disorder caused by a pentanucleotide (ATTCT) repeat expansion in intron 9 of the *ATXN10* gene on chromosome 22q13.3 [1]. The ATTCT repeat is polymorphic, ranging in size from 10 to 32 repeats in the normal population and from 800 to 4500 in mutant alleles [1].

Unlike most forms of inherited ataxias, which often present with other impairments of the central and peripheral nervous system, SCA10 was initially described as a pure cerebellar syndrome [2]. However, a subsequent study showed that a significant proportion of patients present with seizures [3]. This landmark study of four Mexican families revealed the occurrence of additional clinical features, such as sensory polyneuropathy, pyramidal signs, and cognitive and neuropsychiatric abnormalities [3]. The occurrence of these features, particularly

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seizures, is not uniform as a large SCA10 series from Brazil with 60 patients from 10 families described ataxia as the sole manifestation, with seizures detected in a frequency similar to that expected for the general population [4]. In contrast, in a series of 23 SCA10 patients from different Brazilian states, epilepsy was found in 65% of the cases, presenting with tonic-clonic seizures or combinations of myoclonic, complex partial, and generalized tonic-clonic seizures [5].

Nonmotor symptoms (NMS) have been increasingly recognized in a number of neurodegenerative diseases with a burden of disability that parallels or even surpasses that induced by motor symptoms [6]. As NMS have often been poorly recognized and inadequately treated, much of the most recent developments in the investigation of these disorders has focused on the recognition and quantification of NMS, which will form the basis of improved clinical care for these complex cases.

Although NMS have been sparsely investigated in a limited number of SCAs, particularly Machado-Joseph disease (MJD), it has not been systematically studied in SCA10. The aim of the present study was to investigate their presence among cases with a genetic diagnosis of this disorder, comparing the results with the better-delineated clinical profile of MJD patients and a healthy control group.

Methods

Subjects

Subjects were prospectively recruited at the outpatient Movement Disorders Unit of the Federal University of Paraná from February 2012 to October 2014. The unit is a major referral center for SCAs in Southern Brazil. All cases in the SCA10 and MJD groups had clinical and genetically confirmed diagnosis (SCA10 was confirmed by an ATTCT pentanucleotide repeat expansion with more than 32 repeats in the ATXN10 gene in chromosome 22q13 and SCA3 behind the presence of a CAG trinucleotide repeat expansion with more than 51 repeats of the ATXN3 gene in chromosome 14q24.3-q31) or were symptomatic first-degree relatives of genetically confirmed individuals. Age- and gender-matched healthy volunteers, recruited among nonconsanguineous individuals (spouses or caregivers), were invited to participate. Patients with SCA10 and MJD were also matched for gender, age, and disease duration. All patients and controls were older than 18 years of age and entered the study after a cognitive screening using the Mini-mental State Examination (MMSE) with a cutoff score of 24 (adjusted for education, at least 4 years). During the testing process, patients were not on medication that could interfere with the test results, such as antidepressants or benzodiazepines.

This study was approved by the institutional ethics committee of the Federal University of Paraná and all patients and healthy controls signed an informed consent.

Clinical Evaluation of Ataxia

Demographic and clinical data were collected using a standardized protocol, which consisted in (a) systematic review of the medical notes and (b) standardized evaluation of the severity of ataxia using the Brazilian validated Scale for the Assessment and Rating of Ataxia (SARA) [7].

Rating of Nonmotor Symptoms

Patients and controls underwent a detailed neurological evaluation and previously validated questionnaires with emphasis on NMS. All questionnaires were applied by the same examiner. Chronic pain was defined as self-reported pain lasting longer than 3 months with episodes on at least 50% of the days. Pain was clinically classified according to Goetz et al. [8] as musculoskeletal, dystonic, neuropathic, mixed, or unclassified. Autonomic symptoms were assessed using a detailed questionnaire modified from low [9], which included questions regarding presence of syncope, intolerance to cold, excessive sweating, dry mouth or eyes, skin discoloration, and urinary or gastro-intestinal disorders—each symptom was scored on a nominal variable (yes or no) irrespective of severity and the total score was the total number of symptoms. Fatigue was evaluated using the Modified Fatigue Impact Scale for Portuguese (MFIS-BR) (cutoff 38) [10]. Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS) (cutoff 9) [11]. Rapid eye movement (REM) sleep behavior disorder (RBD) was clinically diagnosed with REM Behavior Disorder Screening Questionnaire (RBDSQ) [12]; the presence of restless legs syndrome (RLS) was defined by the international criteria proposed by the International Restless Legs Syndrome Study group and its severity through the Restless Legs Syndrome Rating Scale (IRLS) [13]. Symptoms of depression were evaluated using the Beck Depression Inventory (BDI) (cutoff 13) [14], and symptoms of anxiety were assessed using the Hamilton Anxiety Rating Scale (HAM-A) (cutoff 17) [15]. The Brazilian version of the MMSE [16] was used as a screening tool for general intellectual abilities and served as the exclusion criteria for the study (cutoff 24). Executive functions were evaluated with the Frontal Assessment Battery (FAB) [17]. The semantic verbal fluency (animals) and phonemic (nouns started with letter S) tests were used to assess association fluency, and the Clock Drawing Test (CDT) [18] was used to screen for visuospatial and constructional abilities based on a scoring system from 0 to 15.

Statistical Analysis

Statistical analyses were conducted using the STATA software (StataCorp LP, Texas, USA, http://www.stata.com/). The distribution of all continuous variables was assessed using the Shapiro-Wilk and Shapiro-Francia tests for normality. ANOVA and Kruskal-Wallis tests were used for multiple comparison analysis. To compare the means and medians, *t* Student and Wilcoxon-Mann-Whitney test were used, respectively. The chi-square test and the Fisher exact test were used for analysis of binomial variables. Spearman correlation coefficients were estimated to evaluate the association between two quantitative variables. To compare SCA10 and MJD groups regarding fatigue, sleep disturbances, cognitive function, and psychiatric disorders, linear regression models were adjusted considering SARA score as covariate. Linear regression was used to investigate when genetic status (length of the ATTCT repeat) was related to NMS in the SCA10 group. Differences were considered significant when p was <0.05. Significance level was corrected by Bonferroni for multiple comparisons ($p < 0.017$).

Results

A total of 28 controls, 28 SCA10 patients from 14 unrelated families, and 28 MJD cases from 26 families were included. By study design, age, gender, and disease duration were not significantly different. Age of onset, educational level, mean SARA score, and mean ATTCT and CAG repeat are also described in Table 1. All patients with SCA10 had pure cerebellar ataxia, i.e., they had no additional motor manifestations, such as dystonia or parkinsonism.

Chronic pain was detected in five patients with SCA10 (17.9%), 10 patients with MJD (35.7%), and three controls (10.7%). The only comparison that reached statistical significance was between MJD and healthy controls ($p = 0.03$). Among patients with SCA10, pain was classified as musculoskeletal in three (60%) and the most common localization was in lower limbs in three or lumbar in two patients. Four patients reported daily episodes of pain, one of them continuous throughout the day. The mean visual analog scale score was 7.8 ± 1.6 indicating moderate to severe pain.

Autonomic symptoms were present with varying frequency among patients with SCA10, as shown in Table 2. When comparing the three groups, all autonomic symptoms were more frequent in MJD patients than in SCA10 and controls. The most frequent autonomic symptoms reported by patients with SCA10 were nocturia, excessive sweating, and cold intolerance.

With regard to fatigue, 9 patients with SCA10 presented with MFIS-BR scores above 38. The median score of MFIS-BR in SCA10 patients was 24.5 (IR 14.5–42), versus 35 (IR 26–45.5) in MJD and 16.5 (IR 11–24.5) in controls. The comparison showed a more striking difference when comparing the MJD group with controls ($p < 0.0001$). No significant difference occurred comparing SCA10 and MJD scores. In the physical domain, the difference between the three groups was more important in relation to the cognitive and psychosocial domain, although it was not statistically significant (Table 3).

Daytime sleepiness scores for SCA10 patients were not significantly different from the ones found among MJD cases, but higher than in controls. Eleven SCA10 patients showed an abnormal ESS (above 9). Restless legs syndrome and RBD had low prevalence in SCA10 patients. We found RLS in one patient with SCA10, one healthy control (3.6%), and 10 (35.7%) patients with MJD. RBD was not detected among SCA10 patients and was found in one healthy control (3.6%) and in 12 (42.9%) patients with MJD. The findings related to sleep disorders are presented in Table 3.

Depressive manifestations were present in 16 patients with SCA10. Ten (62%) of them had mild symptoms. The median

Table 1 Clinical and demographic variables in SCA10 patients and controls

		SCA10	MJD	Control	*p**
Gender	No. M/F	13/15	11/17	12/16	0.86
Educational level	Mean ± SD	11.1 ± 4.1	11.6 ± 5.0	11.7 ± 4.0	0.81
Age in years	Mean ± SD	46.8 ± 11.6	49.7 ± 9.7	47.3 ± 12.8	0.60
Age of onset in years	Mean ± SD	31.7 ± 7.6	36.4 ± 7.8	NA	0.02
Disease duration in years	Mean ± SD	15.5 ± 12	13.5 ± 7.3	NA	0.70
SARA	Mean ± SD	9.9 ± 4.5	15.7 ± 7.3	NA	0.0007
MMSE	Median (IQR)	28 (24.5–29)	28 (26.5–29)	29 (28–29.5)	0.25
Genetic data (no. of ATTCT and CAG repeats)	Median (IQR)	1990 (1900–2229)	70 (67–75)	NA	NA

SCA10 spinocerebellar ataxia type 10, *MJD* Machado-Joseph disease, *M* male, *F* female, *SD* standard deviation, *IQR* interquartile range, *NA* not applicable, *SARA* Scale for the Assessment and Rating of Ataxia

*ANOVA and Kruskal-Wallis tests

Table 2 Autonomic symptoms in SCA10 patients and controls

	SCA10 % (*n*)	MJD % (*n*)	Control % (*n*)	SCA10 vs. MJD (*p**)	SCA10 vs. control (*p**)	MJD vs. control (*p**)	SCA10 vs. MJD (*p***)
Syncope	3.6 (1)	7.1 (2)	3.6 (1)	1.0	1.0	1.0	0.53
Cold intolerance	21.4 (6)	50 (14)	21.4 (6)	0.02	1.0	0.03	0.05
Excessive sweating	21.4 (6)	39.3 (11)	21.4 (6)	0.15	1.0	0.14	0.04
Skin discoloration	3.6 (1)	42.9 (12)	7.1 (2)	0.001	1.0	0.004	0.01
Dry mouth	14.3 (4)	25 (7)	10.7 (3)	0.5	1.0	0.29	0.62
Dry eye	0 (0)	3.6 (1)	3.6 (1)	1.0	1.0	1.0	0.99
Excessive salivation	14.3 (4)	28.6 (8)	0 (0)	0.33	0.11	0.004	0.86
Nocturia	28.5 (8)	32.1 (9)	0 (0)	1.0	0.05	0.05	0.10
Urine incontinence	10.7 (3)	39.3 (11)	7.1 (2)	0.03	1.0	0.01	0.17
Urine retention	0 (0)	3.6 (1)	0 (0)	1.0	1.0	1.0	0.99
Anorexia	0 (0)	0 (1)	0 (0)	1.0	1.0	1.0	1.0
Diarrhea	0 (0)	0 (0)	0 (0)	1.0	1.0	1.0	–
Constipation	14.3 (4)	28.6 (8)	14.3 (4)	0.33	1.0	0.33	0.22
Orthostatic hypotension	3.6 (1)	35.7 (10)	3.6 (1)	0.005	1.0	0.005	0.06
≥3 Symptoms	28.6 (8)	78.6 (22)	7.1 (2)	<0.0001	0.04	<0.0001	0.007

SCA10 spinocerebellar ataxia type 10, *MJD* Machado-Joseph disease

*Chi-square test and Fisher exact test; $p < 0.017$, significance level corrected by Bonferroni

**Adjusted for SARA

score of BDI was 12.5 (IR 8.0–19.5) in patients with SCA10, 14.5 (IR 9.5–23.5) in MJD, and 5 (IR 3–10) in controls. Differences were significant for the comparisons between SCA10 and healthy controls ($p = 0.008$) and for MJD and controls ($p = 0.0003$). Anxiety symptoms were present in 9 patients with SCA10. Scores of HAM-A showed a median of 8.5 (IR 4–17) in SCA10 patients, 15 (IR 8–22.5) in MJD, and 7 (IR 4–10) in controls (Table 4).

As shown in Table 4, in all cognitive tests—FAB, semantic verbal fluency, phonemic verbal fluency, and CDT—the performance of healthy controls was better compared with SCA10 patients and MJD, which showed the worst scores. Comparing SCA10 and MJD, the latter group presented worse performance in verbal fluency tests. We observed a tendency toward significance in relation to phonemic verbal fluency, which lost significance when adjusted for SARA. Spearman correlation coefficients were estimated to evaluate the association between cognitive performance and depressive symptoms (Table 5).

In an attempt to investigate the genetic correlates of NMS in SCA10, the length of the ATTCT repeat was correlated to NMS. The results are presented in Table 5.

Table 3 Fatigue and sleep disorders in SCA10 patients and controls

		SCA10	MJD	Control	SCA10 vs. MJD (*p**)	SCA10 vs. control (*p**)	MJD vs. control (*p**)	SCA10 vs. MJD (*p***)
MFIS	Median (IQR)	24.5 (14.5–42)	35 (26–45.5)	16.5 (11–24.5)	0.07	0.03	<0.0001	0.32
MFIS, physical score	Median (IQR)	13 (7.5–23)	22.5 (14.5–27.5)	8.5 (5–13.5)	0.02	0.03	<0.0001	0.08
MFIS, cognitive score	Median (IQR)	6.5 (2.5–13)	6 (2–19)	4 (2–8.5)	0.96	0.18	0.30	0.93
MFIS, psychosocial score	Mean ± SD	4.3 ± 2.9	4.3 ± 2.8	2.9 ± 2.6	0.97	0.06	0.06	0.34
ESS	Mean ± SD	8.2 ± 5.4	7.2 ± 5.3	4.8 ± 3.2	0.49	0.01	0.01	0.75
RLS	*n* (%)	1 (3.6)	10 (35.7)	1 (3.6)	0.005	1.0	0.005	NA
RBD	*n* (%)	0	12 (42.9)	1 (3.6)	<0.001	1.0	0.001	NA

SCA10 spinocerebellar ataxia type 10, *MJD* Machado-Joseph disease, *MFIS* Modified Fatigue Impact Scale, *IQR* interquartile range, *SD* standard deviation, *ESS* Epworth Sleepiness Scale, *RLS* restless legs syndrome, *RBD* REM sleep behavioral disorder, *NA* not applicable

**t* Student, Wilcoxon-Mann-Whitney test, and Fisher exact test; $p < 0.017$, significance level corrected by Bonferroni

**Adjusted for SARA

Table 4 Cognitive and affective performances in SCA10 patients and controls

		SCA10	MJD	Control	SCA10 vs. MJD (p*)	SCA10 vs. control (p*)	MJD vs. control (p*)	SCA10 vs. MJD (p**)
BDI	Median (IQR)	12.5 (9–19.5)	14.5 (9.5–23.5)	5 (3–10)	0.6	0.008	0.0003	0.86
HAM-A	Median (IQR)	8.5 (4–17)	15 (8–22.5)	7 (4–10)	0.04	0.31	0.0008	0.11
FAB	Mean ± SD	13.1 ± 2.7	12.9 ± 2.5	15.1 ± 1.6	0.84	0.001	0.0003	0.35
Verbal fluency - Semantic	Mean ± SD	13.3 ± 2.7	11.5 ± 3.1	14.8 ± 2.8	0.02	0.04	0.0001	0.19
Verbal fluency - Phonemic	Mean ± SD	7.8 ± 3.4	6.2 ± 3.2	11 ± 3.3	0.06	0.001	<0.0001	0.08
CDT	Median (IQR)	13 (12–15)	12 (11–15)	15 (14–15)	0.32	0.007	0.0001	0.82

SCA10 spinocerebellar ataxia type 10, *MJD* Machado-Joseph disease, *FAB* Frontal Assessment Battery, *SD* standard deviation, *IQR* interquartile range, *CDT* Clock Drawing Test, *MMSE* Mini-mental State Examination, *BDI* Beck Depression Inventory, *HAM-A* Hamilton Anxiety Rating Scale

*t Student and Wilcoxon-Mann-Whitney test; $p < 0.017$, significance level corrected by Bonferroni

**Adjusted for SARA

Discussion

This is the first study that systematically assessed NMS in a large number of patients with SCA10, despite their already established presence in other spinocerebellar ataxias, particularly MJD. We found that patients with SCA10 presented higher prevalence of some of the NMS screened, including daytime sleepiness, fatigue, depression, and cognitive disorders. The other NMS evaluated, such as chronic pain, autonomic disorders, RBD, and RLS, were similar to the healthy population. However, all NMS were found more frequently in patients with MJD.

Among the NMS evaluated, chronic pain was found in a similar prevalence to that of the healthy sample. Among the three groups, the report of pain was more frequent in individuals with MJD, a finding already described by França et al. [19]. These authors performed a systematic evaluation of 70 patients with MJD and found chronic pain in almost half of the patients, mainly of musculoskeletal origin. To our knowledge, no other study has systematically addressed this issue in MJD patients. As chronic pain is a disabling condition that may be missed when focusing patient's assessment on motor features of these diseases, it should be actively investigated routinely in all patients.

Autonomic nervous system involvement is another potentially debilitating but often overlooked manifestation of neurodegenerative diseases [20]. In our sample, such symptoms were found with a diverse prevalence in patients with SCA10, however, in the same proportion of healthy individual. On the other hand, the group with MJD had significantly higher frequencies compared to SCA10 cases and healthy controls. Our review of the literature found rates of autonomic symptoms in MJD ranging from 5 to 55%, but no systematic assessment of patients with SCA10 [20, 21]. Autonomic dysfunction is frequently subclinical and often requires identification through additional tests, such as heart rate variability and neurophysiological studies [20].

Sleep complaints have been considered as an important determinant modifier of health-related quality of life in SCAs [22]. Of all NMS evaluated in the study, the frequency of RBD and RLS showed the most significant differences between samples. Our data are consistent with the literature showing a significantly higher frequency of RBD and RLS in the MJD group when compared to the general population, reaching about 50 and 55%, respectively [6, 22, 23]. The pathology of RLS and RBD is unknown, but evidence from previous studies suggests a correlation with dopamine deficiency and degeneration in brainstem structures seen in MJD [22]. In this study, patients with SCA10 and MJD presented higher prevalence of ESS in relation to the healthy sample and no statistically significant difference between the scores of the

Table 5 Correlation between genetic analyses and BDI with nonmotor symptoms in SCA10 patients

Scale	Length of ATTCT repeat		BDI	
	Correlation	p*	Correlation	p*
MFIS-BR	0.18	0.48	–	–
ESS	0.31	0.22	–	–
BDI	−0.11	0.67	–	–
HAM-A	−0.01	0.95	–	–
FAB	−0.06	0.81	−0.15	0.440
Semantic fluency	−0.11	0.67	−0.07	0.710
Phonemic fluency	−0.57	0.01	−0.19	0.324
CDT	0.37	0.14	−0.39	0.042

SCA10 spinocerebellar ataxia type 10, *MFIS-BR* Modified Fatigue Impact Scale for Portuguese, *ESS* Epworth Sleepiness Scale, *BDI* Beck Depression Inventory, *HAM-A* Hamilton Anxiety Rating Scale, *FAB* Frontal Assessment Battery, *CDT* Clock Drawing Test

*Statistical significance was set at $p < 0.05$, Spearman's rank correlation coefficient

two groups of patients with SCAs. Although high frequencies of EDS have also been documented in MJD patients [23, 24], Pedroso et al. [25] showed no difference in ESS scores between MJD and a control group in their series.

Our survey demonstrates total scores of MFIS, as well as the physical domain, higher in the group with SCA10 compared to healthy controls, showing to be a more prevalent NMS than in the healthy population, matched for sex and age. Regarding the group with MJD, the prevalence of fatigue, mainly physical fatigue, is increased compared with healthy controls and SCA10. The specific physiopathology of fatigue remains unknown but is presumably multifactorial, representing a confluence of physiological and behavioral factors [24]. Whereas cerebellum plays an important role in action control and motor learning, as well as the nonmotor functions of the cerebellum, related to attention, executive control, learning, language, and visuospatial abilities, are increasingly identified [26], it could also play a relevant pattern in the model of central fatigue [24].

The Cerebellar Cognitive Affective Syndrome (CCAS) is a well-known condition, characterized by disturbances in executive function, spatial cognition, language, and emotional regulation of behavior [27]. CCAS is reported to neural circuits linking prefrontal, posterior parietal, superior temporal, and limbic cortices with the cerebellum [27]. In fact, our study proposes that patients with SCA10 have mild cognitive impairments, lower than those found in patients with MJD. Roeske et al. [28] studied the cognitive profile of MJD patients over a period of 3.5 years, and they found a deterioration of verbal learning and verbal and figural memory. Their data suggests that progressive cognitive impairment is part of clinical spectrum of MJD and may be caused by progressive extracerebellar pathology or even cerebellar-cerebral disconnection. It is important to note that CDT was impaired by the depressive symptoms present in our sample with SCA10. Therefore, further studies are needed to confirm this suspicion.

As expected, the prevalence of depressive syndromes and anxiety in patients with spinocerebellar ataxia was higher than estimates from healthy control, and median scores of BDI and HAM-A were higher in MJD compared with the SCA10 group. Probably, mood disorders are related to CCAS, more exuberant in patients with MJD compared to the group with SCA10. In addition, symptoms such as depression and anxiety can be reactional to the degree of motor involvement. Depressive symptoms are very common and significantly impair the subjective well-being of ataxic patients [29]. A survey performed in 526 SCA patients from the European Integrated Project on Spinocerebellar Ataxias (EUROSCA) clinical group found that 46% of patients exhibited depression/anxiety problems [30].

The major strengths of this study include the systematic and objective assessment of NMS in a large sample of patients with SCA10. We chose to study both MJD and a healthy control group for comparison due to the well-known presence of these symptoms in patients with MJD, and the supposed lack thereof in healthy controls. A main limitation is the lack of specific tests to assess autonomic function or confirm the reported sleep disorders; future studies including electromyography and polysomnography might also provide additional insights. Also, our study design carries a floor effect bias in terms of cognitive findings, due to the fact that cases with MMSE below the cutoff were excluded to ensure that patients would understand the other questionnaires. In addition, some employees' tests such as verbal fluency test may be affected by dysarthria in patients with higher neurological involvement. Additional studies should include a more detailed cognitive evaluation.

Nonmotor symptoms were more frequent and severe in MJD than in SCA10 patients. This could be related to disease severity, considering that patients with MJD in this cohort were more disabled than those with SCA10. However, the adjustment of the variables for SARA did not confirm this hypothesis. In this way, we believe be a true disease-specific phenomenon related to the more widespread central nervous system and Purkinje damage found in MJD.

Overall, this study made possible the identification of important NMS in patients with SCA10 to be tested in future studies and alerted to the systematic search for these symptoms in daily clinical practice in order to optimize treatment and improve the quality of life of these patients.

Compliance with Ethical Standards This study was approved by the institutional ethics committee of the Federal University of Paraná and all patients and healthy controls signed an informed consent.

Conflict of Interest TA was supported by NIH grant NS083564.

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