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ORIGINAL PAPER

Non-motor and Extracerebellar Features in Spinocerebellar Ataxia Type 2

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Abstract Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant degenerative disease. Pathological studies have demonstrated not only cerebellar and brainstem atrophy, but substantia nigra, motoneurons, basal ganglia, thalamus, and peripheral nerves involvement. These findings may explain non-motor and extra-cerebellar features in SCA2. We accessed the non-motor symptoms and extra-cerebellar signs in SCA2 patients in order to provide a better understanding on pathophysiological mechanisms and natural history of brain degeneration in the disease. Thirty-three SCA2 patients were evaluated and compared with 26 healthy subjects. We investigated the following variables: sleep disorders, cognitive deficit, olfactory impairment, urinary dysfunction, psychiatric symptoms, cramps, pain, movement disorders, and weight loss. SCA2 had a high frequency of REM sleep behavior disorder (48.48 %, $N=16$) as well as excessive daytime sleepiness (42.42 %, $N=14$). Chorea was present in 15.15 % ($N=5$), dystonia in 27.27 % ($N=9$), and parkinsonism in 27.27 % ($N=9$). Slow saccadic pursuit was present in 87.87 % ($N=29$) and ophtalmoparesis in 78.78 % ($N=26$) of patients. Regarding sleep disorders, 18.18 % ($N=6$) of patients had restless leg syndrome. Dysphagia was present in 39.39 % ($N=13$), weight loss 24.24 % ($N=8$), and urinary dysfunction 27.27 % ($N=9$). Cramps was present in only 6 % of patients ($N=2$). This study highlighted the high frequency of non-motor symptoms and extra-cerebellar signs in SCA2. Our findings demonstrate the widespread of nervous system involvement in SCA2 patients and contribute to better understand the natural history of brain degeneration in this genetic condition.

Keywords Spinocerebellar ataxia type 2 · SCA2 · Non-motor symptoms · Extra-cerebellar signs

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Introduction

Spinocerebellar ataxias (SCAs) are defined as a group of autosomal dominant ataxic disorders caused by degeneration of the cerebellum and its afferent and efferent connections [1]. SCAs have a wide range of neurological symptoms including axial and appendicular ataxia, dysarthria, oculomotor disturbances, extrapyramidal signs, and several non-motor clinical manifestations, such as retinopathy, optic atrophy, peripheral neuropathy, sphincter disturbances, cognitive impairment, and epilepsy [2, 3]. Anatomical, physiological, clinical, and functional neuroimaging data reinforce the idea of a degenerative process involving extra-cerebellar regions of the nervous system in several SCA subtypes [4–6]. Interestingly, some reports have recently described a pre-clinical stage in SCA, similar to the model studied in Parkinson's disease [7, 8].

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant inherited degenerative disease and is caused by an abnormal expansion of a CAG repeat in ataxin-2 gene, located on chromosome 12q. Clinical features are usually comprised by adult onset progressive ataxia, slow saccadic eye movements, and peripheral neuropathy [9]. Other symptoms and signs may include parkinsonism, cognitive impairment, and amyotrophy. SCA2 is among the most frequent SCA worldwide, together with SCA1, SCA3, and SCA6 [9]. Pathological studies on SCA2 have demonstrated cerebellar and brainstem atrophy, combined with substantia nigra, motor neurons, basal ganglia, thalamus, and peripheral nerves losses [4].

Degenerative process besides the cerebellum may explain non-motor and extra-cerebellar features in SCA2 [4]. Non-motor and extra-cerebellar features were frequently described in SCA3, but were rarely described in SCA2 [2]. The most common ones include sleep disorders, cognitive deficits, dysautonomia, olfactory dysfunction, neuropathy, parkinsonism, chorea, and motor neuron disease [10–13]. The prodromal phase of SCA2 has already been studied in non-ataxic patients [14]. However, the description of non-motor and extra-cerebellar features in SCA2 is sporadically reported.

In this article, we aimed to access the non-motor symptoms and extra-cerebellar signs in a large sample of SCA2 patients in order to provide a better understanding on pathophysiological mechanisms and natural history of brain degeneration in the disease.

Patients and Methods

Patients and Subjects

Thirty-three clinically and molecularly proven SCA2 patients agreed to participate in this study. Nine families were evaluated at the Ataxia Unit, Universidade Federal de São Paulo, and one family in a rural area of Acre state at the North side of Brazil. Twenty-six healthy, unrelated subjects were enrolled as the control group. This study was approved by our Institutional Ethics Committee and a written informed consent was obtained from all patients and control subjects.

Clinical Protocol

A structured interview was performed, asking for age at onset (AO) of first symptom, disease duration (DD), and subjective information such as weight, urinary dysfunction, and cramps. Weight loss was considered positive and significant when there was a loss of 10 % of body weight over a 6-month period, according to the patient's report. Urinary incontinence or retention, cramps, and muscle pain were investigated by *yes* or *no* questions. Molecular studies were previously done in all subjects and were reported elsewhere [15]. After the interview, patients were evaluated by the following clinical instruments: "Scale for the Assessment and Rate of Ataxia" (SARA) in order to evaluate ataxia severity, and "Inventory of Non-ataxia symptoms" (INAS) for evaluation of non-motor and extracerebellar features [16, 17]. In the same day of the motor evaluation, non-motor features were assessed by the specific clinical scales, as follows.

Sleep disorders—REM sleep behavior disorders (RBD), restless legs syndrome (RLS), and excessive daytime sleepiness (EDS)—were evaluated by RBD Screening Questionnaire (RBDSQ) and Epworth Sleepiness Scale (ESS) [18, 19]. RBDSQ is a five-point scale. Those who fulfilled the criteria of the five questions were considered to have clinically defined RBD [18]. ESS is a n-point scale where a cut-off of 10 or greater was set for the diagnosis of excessive daytime sleepiness (EDS) [18].

Psychiatric symptoms (depression and anxiety) and cognitive impairment were evaluated by Beck Depression Inventory (BDI), Hamilton Anxiety Scale (HAS), and mini-mental state examination (MMSE). In order to evaluate olfactory dysfunction, Sniffin's Sticks (SS-16) were used according to standard reported elsewhere [20].

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Science version 22. Numerical data were presented as mean and standard deviation (SD). Categorical variables were expressed as total number and percentage. Subjects were divided into two groups: a healthy control group and SCA2 patients. Comparisons between groups were performed using chi-square test or Fisher's exact test for categorical data and using two-sample t test or Mann-Whitney test for continuous variables. Among patients with SCA2, Spearman's correlation test was performed to calculate the strength of association of the following variables: AO, DD, ataxia severity (SARA), CAG repeat length, SS-16, HAD, BDI, ESS, and RBDSQ. A subgroup analysis was also performed in patients with SCA2 regarding the presence of parkinsonism. Since this was an exploratory study, a p value <0.05 was chosen and corrections for repeated measurements were not applied.

Results

Table 1 summarizes the clinical and demographic data from the 33 patients with SCA2 and 26 healthy control group. Patients with SCA2 have significantly more anxiety and depression symptoms as well as a significant poorest performance in the Sniffin's test (SS-16).

Regarding the correlation analyses, the CAG repeat length at the expanded allele was strongly correlated with AO (cc:

Table 1 Clinical and demographic characteristics of patients with SCA2 compared with health control group

	SCA2 patients ($N=33$)	Control group ($N=26$)	P value
Age (years); mean ± SD	40.69 ± 13.56	39.49 ± 12.74	0.660
Gender (female to male ratio; % female)	19:7; 73 %	17:16; 51.50 %	0.078
Disease duration (years)	8.27 ± 6.20		
Age of disease onset (years); mean ± SD	32.87 ± 14.02		
Years of education; mean ± SD	8 ± 3.93	9.7 ± 3.34	
MMSE; mean ± SD	23.63 ± 4.52	23.33 ± 9.58	0.12
HAD; mean ± SD	12.21 ± 7.71	8.25 ± 9.20	0.031*
BDI; mean ± SD	15.13 ± 10.56	6.88 ± 13.49	0.001*
SARA; mean ± SD	16.80 ± 12.20		
ESS; mean ± SD	9.03 ± 4.06	7.88 ± 4.26	0.26
RBDSQ; mean ± SD	4.87 ± 2.95		
IRLSRS; *N*; (%)	5; 18.51 %	1; 4.15 %	0.223
SS-16; mean ± SD	10.28 ± 2.32	12.04 ± 2.01	0.006*

SD standard deviation, *MMSE* mini-mental state examination, *HAD* Hospital Anxiety and Depression Scale, *BDI* Beck Depression Inventory, *SARA* Scale for the Assessment and Rating of Ataxia, *ESS* Epworth Sleepiness Scale, *RBDSQ* REM Behavior Disorder Sleepiness Scale, *IRLSRS* International Restless Leg Syndrome Rating Scale

* Statistically significant p value

−0.911; $p<0.001$). In addition, SS-16 was correlated with BDI (cc: −0.560; $p<0.001$), with HAD (cc: −0.36; $p=0.036$), with RBDSQ (−0.369; $p=0.007$), and with DD (cc: −0.440; $p=0.035$).

Table 2 describes the main clinical symptoms and neurological signs of all patients with SCA2 and summarizes data from each patient. SCA2 had a high frequency of RBD (48.48 %, $N=16$) as well as EDS (42.42 %, $N=14$). Regarding movement disorders, cerebellar ataxia was present in all patients ($N=33$), dystonia in 27.27 % ($N=9$), Parkinsonism in 27.27 % ($N=9$), and chorea in 15.15 % ($N=5$). Chorea was present only in patients with other movement disorders (dystonia, parkinsonism) rather than ataxia in our sample. Neuro-ophthalmologic evaluation disclosed slow saccadic pursuit in 87.87 % ($N=29$) and ophtalmoparesis in 78.78 % ($N=26$) of patients. Urinary dysfunction was present in 27.27 % ($N=9$), all of which had at least one neuro-ophthalmologic pathologic finding (opthalmoparesis or slow saccadic pursuits). Regarding sleep disorders, 18.18 % ($N=6$) of patients had RLS. Dysphagia was present in 42.42 % ($N=14$) and weight loss in 27.27 % ($N=9$). The majority of patients (88.8 %, $N=8$) with significant weight loss had dysphagia, disclosing thus an important directly positive correlation. Spasticity was present in 15.15 % ($N=5$), all of which presented also opthalmoparesis or abnormal saccades and dysphagia. Cramps were present in only 6 % of patients ($N=2$). There was no evidence of a different clinical profile in patients attending at the Ataxia Unit and the other from Acre State.

Table 2 Summary of clinical data from each SCA2 patient ($n=33$)

Clinical manifestation	Frequency; *N* (%)
REM behavior disorder	16 (48.48)
Excessive daytime sleepiness	14 (42.42)
Restless leg syndrome	5 (15.15)
Parkinsonism	9 (27.27)
Dystonia	9 (27.27)
Chorea	5 (15.15)
Cramps	2 (6.06)
Saccades abnormalities	29 (87.87)
Spasticity	5 (15.15)
Ophthalmoparesis	26 (78.78)
Urinary dysfunction	9 (27.27)
Dyphagia	13 (39.39)
Weight loss	8 (24.24)

Table 3 describes the subgroup analysis of patients with SCA2 regarding the presence of parkinsonism. Patients with SCA2 and parkinsonism had significantly longer disease duration, higher scores of SARA, more depressive symptoms, and worse performed on MMSE and SS-16. On the contrary, the presence of parkinsonism was not significantly associated with RLS RBDSQ or ESS.

Discussion

In this study, we observed a high frequency of non-motor symptoms and other motor manifestation in SCA2 patients beyond cerebellar signs. These findings reinforce that SCA2 represents a more widespread condition, affecting other regions of the nervous system besides the cerebellum and spinocerebellar pathways. Based on previous anatomical and pathological studies, Fig. 1 summarizes the possible correlation between clinical features and the correspondent nervous system affected area in SCA2 patients.

Table 3 Clinical and demographic analysis of the SCA2 patients regarding the presence of parkinsonism

	Parkinsonism ($N = 9$)	No parkinsonism ($N = 24$)	P value
Age (years); mean ± SD	42.26 ± 12.64	40.10 ± 14.10	0.766
Gender (female to male ratio; % female)	6:3; 66.66 %	11:13; 45.83 %	0.438
Disease duration (years); mean ± SD	13.29 ± 7.38	6.42 ± 4.68	0.025*
Age of disease onset (years); mean ± SD	27.77 ± 14.75	34.75 ± 13.66	0.364
CAG repetition number	44.88 ± 3.52	42.45 ± 3.64	0.185
Years of education; mean ± SD	7.67 ± 3.88	8.09 ± 4.03	0.937
MMSE; mean ± SD	18.60 ± 6.22	24.77 ± 3.25	0.033*
HAD; mean ± SD	12.21 ± 7.71	8.25 ± 9.20	0.636
BDI; mean ± SD	23.86 ± 10.10	12.48 ± 9.36	0.008*
SARA; mean ± SD	30.11 ± 10.14	11.81 ± 8.73	<0.001*
ESS; mean ± SD	10.25 ± 3.84	8.61 ± 4.13	0.275
RBDSQ; mean ± SD	6.25 ± 3.57	4.39 ± 2.62	0.132
IRLSRS; *N*; (%)	0; 0 %	5; 20.83 %	0.296
SS-16; mean ± SD	8.29 ± 2.36	10.91 ± 1.97	0.013*

SD standard deviation, *MMSE* mini-mental state examination, *HAD* Hospital Anxiety and Depression Scale, *BDI* Beck Depression Inventory, *SARA* Scale for the Assessment and Rating of Ataxia, *ESS* Epworth Sleepiness Scale, *RBDSQ* REM Behavior Disorder Sleepiness Scale, *IRLSRS* International Restless Leg Syndrome Rating Scale

* Statistically significant p value

Severe and consistent neuronal loss in cholinergic basal forebrain nuclei have been described in patients with SCA2, which may explain the cognitive deficits [21]. In addition, dopaminergic deficits in functional MRI have also been

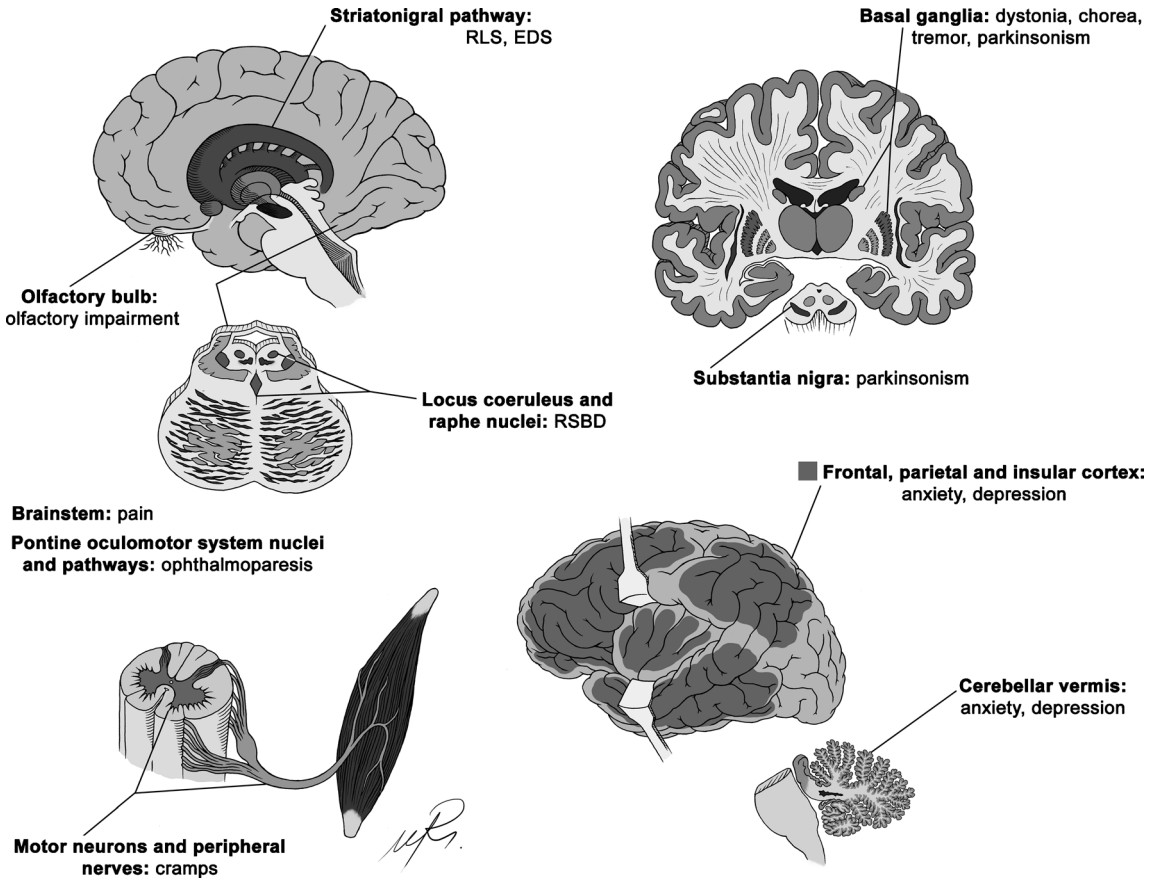

Fig. 1 Summary of the possible correlation between clinical features and the correspondent nervous system affected area in SCA2 patients. Some regions are presumed affected and may justify the non-motor symptoms in SCA2 patients. *RLS* restless legs syndrome, *EDS* excessive daytime sleepiness, *RSBD* REM sleep behavior disorders

reported in patients with SCA2, consistent with the presence of parkinsonism in some patients [22]. Moreover, basal ganglia involvement may explain the high frequency of movement disorders observed in SCA2 patients, such as parkinsonism, chorea, dystonia, and tremor [23, 24]. Parkinsonism in SCAs has geographic differences in prevalence, and levodopa response has been described in patients with SCA2, SCA3, and SCA17 [24–26].

Taking into account that nigrostriatal dopaminergic dysfunction has been implicated in the pathophysiology of idiopathic RLS and RBD, it has been postulated that both sleep complaints might be related to nigrostriatal dopaminergic dysfunction in SCA3 [27]. Considering that we observed similar results in SCA2, with high frequency of RBD (48 %) and to a lesser extent RLS (15 %), it is feasible that similar pathophysiological mechanisms may occur in SCA2 and SCA3. Furthermore, EDS was statistically significant in our SCA2 series. EDS, a frequent symptom in PD, has also been reported in SCA3, but the pathophysiological mechanisms involved are unclear [27–29]. In addition, other sleep disorders such as insomnia and periodic limn movements have also been described in SCA2 [10].

Olfactory impairment has already been described in patients with SCA2 [12]. The pathophysiological mechanism of hyposmia in SCA2 is poorly understood, but cerebellar structures, extra-cerebellar lesions, and brainstem involvement may explain in the olfactory impairment. Moreover, cognitive impairment is well-known to influence olfactory function [30]. Our results suggest that hyposmia was related either to DD as to psychiatric and to RBD manifestations, in our cohort. In addition, patients with parkinsonism had a poorest performance on olfactory test. We hypothesized that a common pathological substract or pathophysiological mechanism may underlie olfactory, sleep, and maybe even parkinsonian manifestations, in SCA2.

Some data have demonstrated autonomic failure in SCA2 patients, and the symptoms may be comprised by heart rate variability, urinary problems, gastrointestinal dysfunction, and others [31, 32]. In our series, urinary dysfunction was present in almost one third of SCA2 patients. Autonomic failure may be related to peripheral and central nervous system regulating sympathetic and parasympathetic function [31]. Cramps were observed only in two SCA2 patients of our series (6 %), in opposite to a previous study, that evaluated SCA2 carriers without cerebellar signs and 81 % referred cramps [33]. Weight loss was prospectively evaluated in SCA3, but not in SCA2 [34]. In our series, a quarter of SCA2 patients had significant weight loss during the disease progression.

Recently, Roderick et al. have proposed a new SCA concept that better defines the asymptomatic, preclinical, and ataxic stages. In this review article, the authors concluded that the preclinical stage in SCA is characterized by subtle central and peripheral nervous system changes [7]. Extracerebellar features, impairment in structural brain regions, functional brain imaging changes, and abnormal neurophysiologic measurements may be present before ataxia [7, 8, 30, 31]. This data will help to understand the pathogenesis of the different SCA subtypes and to determine the optimal point for future therapeutic trials [7]. Therefore, recognizing non-motor and extracerebellar signs in SCA patients may be the paramount in a step of preclinical stage characterization.

This article has some limitations. Firstly, we did not perform polysomnography, functional imaging or *post mortem* studies in our SCA2 patients, and a correlation between the non-motor symptoms and other brain areas are only presumptive. Second, since it is a transversal study, we are unaware whether non-motor and extra-cerebellar features developed before the ataxia. Finally, we did not include a quality of life questionnaire aiming to determine the influence of these symptoms and signs in SCA2 patients.

In conclusion, this study highlighted the high frequency of non-motor symptoms and extra-cerebellar signs in SCA2 patients: sleep disorders, cognitive deficit, olfactory impairment, urinary dysfunction, psychiatric symptoms, cramps, pain, movement disorders, and weight loss. Many of these symptoms and signs are potentially treatable and deserve attention. Our findings demonstrate the widespread of central and peripheral nervous system involvement in SCA2 patients and may contribute to better understand the natural history of brain degeneration in this genetic condition.

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Authors' Contributions 1. Research project: A. Conception, B. Organization, C. Execution
2. Genetic evaluation: A. Execution
3. Clinical evaluation: A. Conception, B. Execution
4. Manuscript: A. Writing of the first draft, B. Review and Critique
Pedroso JL: 1A, 1B, 1C, 3A, 3B, 4A, 4B
Braga-Neto P: 1A, 1B, 1C, 3A, 3B, 4A, 4B
Bezerra MLE: 1A, 1B, 1C, 3A, 3B
Abrahão A: 1A, 1B, 1C, 3A, 3B
Albuquerque MVC: 1A, 1B, 1C, 3A, 3B
Rezende Filho FM: 3A, 3B, 4B
Souza PVS: 1A, 1B, 1C
Pinto WBVR: 1A, 1B, 1C
Borges Junior FRP: 1A, 1B, 1C, 3A, 3B
Saraiva-Pereira ML: 2A, 4A, 4B
Jardim LB: 2A, 4A, 4B
Barsottini OGP: 1A, 1B, 1C, 3A, 3B, 4A, 4B

Compliance with Ethical Standards Full consent was obtained from the patients to be enrolled in this study. Our Institutional Ethics Committee approved this study.

Conflict of Interest The authors declare that they have no competing interests.

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