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Dystonia and ataxia progression in spinocerebellar ataxias

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Author contributions

Dr. Kuo (PHK): statistical interpretation, writing the manuscript, critical revision of the manuscript for important intellectual content.
Dr. Gan: writing the manuscript, critical revision of the manuscript for important intellectual content.
Dr. Wang: study concept and design, statistical analysis and interpretation, critical revision of the manuscript for important intellectual content.
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Disclosure

Dr. Zesiewicz has served as a clinical advisor for Steminent Biotherapeutics, and she has received travel reimbursement from the department of neurology at University of Southern Florida; has received travel reimbursement for a Biohaven Pharmaceuticals meeting. Dr. Zesiewicz has served on the editorial board for *Neurodegenerative Disease Management* and *Tremor and other Hyperkinetic Movements*, and has received research support for her division for approximately 20 clinical trials for Parkinson's disease, Friedreich's ataxia, and spinocerebellar ataxias. Dr. Zesiewicz's division is a site in a multi-site trial of Parkinson's disease patients with the LRRK2 mutation and is sponsored by the National Institutes of Health but funded by Emory University. The rest authors report no conflicts of interest.

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Abstract

Background—Dystonia is a common feature in spinocerebellar ataxias (SCAs). Whether the presence of dystonia is associated with different rate of ataxia progression is not known.

Objectives—To study clinical characteristics and ataxia progression in SCAs with and without dystonia.

Methods—We studied 334 participants with SCA 1, 2, 3 and 6 from the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) and compared the clinical characteristics of SCAs with and without dystonia. We repeatedly measured ataxia progression by the Scale for Assessment and Rating of Ataxia every 6 months for 2 years. Regression models were employed to study the association between dystonia and ataxia progression after adjusting for age, sex and pathological CAG repeats. We used logistic regression to analyze the impact of different repeat expansion genes on dystonia in SCAs.

Results—Dystonia was most commonly observed in SCA3, followed by SCA2, SCA1, and SCA6. Dystonia was associated with longer CAG repeats in SCA3. The CAG repeat number in *TBP* normal alleles appeared to modify the presence of dystonia in SCA1. The presence of dystonia was associated with higher SARA scores in SCA1, 2, and 3. Although relatively rare in SCA6, the presence of dystonia was associated with slower progression of ataxia.

Conclusions—The presence of dystonia is associated with greater severity of ataxia in SCA1, 2, and 3, but predictive of a slower progression in SCA6. Complex genetic interactions among repeat expansion genes can lead to diverse clinical symptoms and progression in SCAs.

Keywords

Spinocerebellar ataxia; Dystonia; Trinucleotide repeat; Modifier

1. Introduction

Spinocerebellar ataxias (SCAs) are a group of autosomal dominant cerebellar disorders, and among them SCA1, 2, 3, and 6 are the most common subtypes. In addition to ataxia, patients with SCA often have other movement disorders. Dystonia is one of the most common co-existing movement disorders in SCAs, especially in SCA3 [1–8]. The genetic underpinning for dystonia in SCAs has not been studied extensively. Although the pathological CAG repeat number per se is the major determinant [9], other repeat expansion genes also play a role in the onset age of ataxia, suggesting the underlying complex interaction among repeat expansion genes [10,11]. The presence of dystonia is also possibly driven by the complex gene-gene interaction and thus leads to diverse clinical presentations in SCAs.

The concept of clinical subtypes has been extensively studied in Parkinson's disease (PD), for which tremor-predominant PD is of slower disease progression than postural instability and gait difficulty (PIGD) predominant PD [12]. Besides, the clinical subtypes of SCA2, SCA3, and dentatorubral-pallidoluysian atrophy (DRPLA) had also been reported to predict the clinical presentation and prognosis [6,13,14]. Likewise, we hypothesize that dystonia in SCAs reflects a different underlying genetic complex and suggests a different rate of ataxia progression or prognosis. Therefore, we tested these hypotheses by studying cohort of SCA patients from the Clinical Research Consortium for SCAs (CRC-SCA), the largest longitudinal SCA cohort in the North America.

2. Patients and methods

2.1. Patient selection

Three hundred and forty-five SCA patients were enrolled in the natural history study of CRC-SCA [15], and the baseline characteristics and clinical progression had been investigated thoroughly in this cohort [15–19]. We excluded 11 patients without information on the dystonic symptom, so we analyzed on 334 patients. These patients were evaluated by ataxia specialists during January 2010 to August 2012, from 12 participating centers in the United States, including Columbia University, Emory University, Johns Hopkins University, Massachusetts General Hospital, University of California Los Angeles, University of California San Francisco, University of Chicago, University of Florida, University of Michigan, University of Minnesota, University of South Florida, and University of Utah. These SCA patients were either self-referred to ataxia clinics or referred by community physicians, local support groups, and the National Ataxia Foundation. The local institutional review boards approved the uniform study protocol and informed consents were obtained from all participants. The inclusion criteria were the following: (1) the presence of ataxia, (2) definite genetic diagnosis of SCA1, 2, 3, or 6 either for the subject or affected family members with ataxia, (3) willingness of participation, and (4) age of 6 years and older. The exclusion criteria were the following: (1) known recessive, X-linked, or mitochondrial

ataxia, (2) exclusion of SCA1, 2, 3, and 6 by genetic tests, and (3) concomitant disorders that affect ataxia measurement used in this study.

Every patient received face-to-face interviews and neurological examinations by ataxia specialists, and the presence of dystonia was determined at the baseline clinical visit. All our ataxia specialists were well trained neurologists, and they were experts in the field of ataxia and movement disorders. During the neurological examination, dystonia was recognized by the sustained movement, either twisting or repetitive, with co-contraction of agonists and antagonists, and the movement might progress to prolonged abnormal posture [20–22]. We examined patients at rest, action, and walking, and we looked for twisted or repetitive pattern of dystonia in different body parts including face, neck, arms, legs and trunk [20–22]. Specifically, action dystonia of the hands was evaluated with the repeated finger-nose maneuver and also with holding the arms stretched while sitting for 10 s. The age of onset was defined as the age when the patient first noted gait ataxia during walking in ordinary circumstances. All participants were asked to provide their blood samples for SCA genotyping. The studied subjects were followed every six months until two years from the baseline visit or until the end of August 2012 when the study was closed. In each visit, a trained ataxia expert scored the severity of ataxia by the Scale for Assessment and Rating of Ataxia (SARA) [23].

2.2. Genetic testing

DNA samples from blood were obtained from subjects, and the repeat expansions of the 9 genes, including *ATXN1* (SCA1), *ATXN2* (SCA2), *ATXN3* (SCA3), *CACNA1A* (SCA6), *ATXN7* (SCA7), *ATXN10* (SCA10), *PP2R2B* (SCA12), *TBP* (SCA17), and *FRDA* (Friedreich's ataxia, FA), were determined in Dr. Stefan Pulst's laboratory. The Qiagen FlexiGene DNA Kit (Qiagen, Hilden, Germany) was used to extract DNA and repeat expansions were determined by multiplex polymerase chain reaction (PCR), followed by capillary electrophoresis with internal standards. Re-genotyping and Sanger sequencing were performed for verification of repeat length in 10% of all samples.

2.3. Predictive variables

Dystonia was treated as a dichotomous variable or major predictor [19]. The repeat numbers of 9 genes specified above were entered into the model to test whether the presence of dystonia was influenced by other SCA repeat expansion genes. Since there are two alleles in each gene, we chose the longer repeat allele for our analyses.

2.4. Outcome variables

We used SARA to measure the severity of ataxia symptoms. SARA ranges from 0 to 40, and higher SARA scores reflected worse motor performance. This outcome measure was treated as continuous variables. The presence of dystonia as a dichotomous variable was the outcome measurement when testing the gene-gene complex interaction.

2.5. Statistical analysis

SCA 1, 2, 3, and 6 were treated as four independent cohorts and analyzed independently. We separated each type of SCAs into two groups, depending on whether they had dystonia or not at baseline.

We used Chi-square tests to compare the percentage of SCAs with dystonia. We assessed whether demographic features of patients with SCAs were normally distributed by Kolmogorov–Smirnov test. For normally distributed variables, we used Student's t-test, and for non-normally distributed variables, we used the Mann–Whitney *U* test for the comparison of basic demographics.

We employed logistic regression to investigate whether different SCA repeat expansion genes would influence the presence of dystonia in SCAs. These methods have been used extensively in genetic modification studies for SCAs [6,11].

The longitudinal analyses of ataxia progression of the two SCA groups (dystonia vs. non-dystonia) during the 2-year observation were conducted by entering the interaction terms (dystonia x time) into the generalized estimating equation (GEE) models, which allow us to study the changes of time-varying variables between groups. Coefficients of the interaction terms reflected how the rate of motor progression differed by the presence of dystonia in SCAs. All statistical analyses were performed using SPSS software (version 23).

3. Results

We studied 334 SCA patients in CRC-SCA (SCA1: 58, SCA2: 72, SCA3: 134, SCA6: 70), and we compared the percentage of dystonia in different types of SCAs (Table 1 and Supplement Table 1). Dystonia was more prevalent in patients with SCA3 (24.6%), followed by SCA2 (18.1%), SCA1 (12.1%), and SCA6 (8.6%). We next compared the clinical characteristics between SCAs with and without dystonia (Table 2). Interestingly, SCA3 with dystonia had 10-year earlier age of onset (31.06 ± 10.94 vs. 41.35 ± 11.11, $p < 0.001$) and longer CAG repeat numbers (73.63 ± 4.54 vs. 70.04 ± 3.70, $p < 0.001$). The clinical characteristics between dystonia and non-dystonia groups did not differ in SCA1, 2, and 6.

In the logistic regression analyses of the influence of genes with repeat expansions on the presence of dystonia in SCAs, we found that repeat expansions in genes either in the pathological SCA genes or other genes with repeat expansions can modify the presence of dystonia (Table 3). In our models, SCA3 patients with longer repeats in *ATXN3* had a higher chance of dystonia (OR = 1.35, $p = 0.018$). SCA1 with longer repeats in *TBP* had a lower rate of dystonia (OR = 0.28, $p = 0.040$). Dystonia in SCA2 and SCA6 was not influenced by the trinucleotide or pentanucleotide repeats.

Of the 334 patients (with 59 dystonia patiens), 14 patients (with 2 dystonia patients) were followed for 24 months, 72 patients (with 12 dystonia patients) were followed for 18 months, 66 patients (with 8 dystonia patients) were followed for 12 months, and 78 patients (with 12 dystonia patients) were followed for 6 months, and 104 patients (with 25 dystonia patients) had only the baseline visit [15]. The longitudinal data of SARA were analyzed by

GEE model. Longer CAG repeat length is associated with faster ataxia progression in all SCAs. The presence of dystonia was associated with higher SARA scores in SCA1, 2, and 3 but did not change the rate of the ataxia progression in these SCAs. On the other hand, dystonia was associated with a slower rate of ataxia progression in SCA6 ($\beta = -1.87$, $p = 0.020$) (Table 4).

4. Discussion

In the present study, we found that dystonia was a common feature in SCA3, compatible with previous study, including Brazilian cohorts [1,11], an Indian cohort [4], a Spanish cohort [7], and a German cohort [8], particularly those with longer CAG repeats. The presence of dystonia in SCA1 was associated with a shorter CAG repeat length of *TBP*; otherwise, other repeat expansion genes did not seem to play significant roles on dystonia. Dystonia was associated with more severe ataxia in SCA1, 2, and 3 but did not change the rate of ataxia progression. On the other hand, the presence of dystonia was associated with a slower rate of ataxia progression in SCA6.

The causes of dystonia in SCAs are not entirely clear although our study suggests some genetic modifiers could play a role. Dystonia in SCAs could result from the cerebellar pathology and extra-cerebellar involvement [24–28]. The brain circuitry involved in dystonia has been reported in the cerebellum and its connection to the brainstem, cervical spinal cord, thalamus, and motor cortex [5,24–29]. Alternatively, dystonia might come from the extra-cerebellar regions, including basal ganglia, and the alterations of basal ganglia have been identified in SCAs based on the volumetric magnetic resonance imaging (MRI) studies [5], dopamine transporter scan studies [30], and postmortem pathological examination [31–33]. The presence of dystonia might indicate the preferential involvement of different cerebellar or extra-cerebellar circuits and thus represent different subtypes of respective SCAs.

The prevalence of dystonia in SCA has been reported to be 13% in SCA1, 14% in SCA2, 24% in SCA3, and 5% in SCA6 in the EUROSCA cohort [34], which is consistent with our study. Also, our study confirmed the previous studies that a longer CAG repeat length in SCA3 are more likely to be associated with dystonia [5,11,13].

Interestingly, we found that dystonia was associated with more severe ataxia in SCA1, 2, and 3 but SCA6. On the other hand, dystonia can predict a slower ataxia progression in SCA6 but not in SCA1, 2, and 3. These discrepancies might be related to different disease mechanisms. The neuronal toxicity of SCA6 is due to defective α1ACT, a product of the bi-cistronic transcript of *CACNA1A* gene, which is unique among CAG-repeat SCAs [35]. In addition, SCA6 also has different neuropathological features compared to SCA1, 2, and 3. While SCA1, 2, and 3 usually have extra-cerebellar involvement, SCA6 is relatively restricted to the cerebellar cortex [36]. Therefore, patients of SCA6 with dystonia might represent a subtype of SCA6 with additional basal ganglia involvement, leading to different clinical course. Another possibility is that patients of SCA6 with dystonia might represent a dysfunctional compensatory mechanism for the loss of cerebellar Purkinje cells. These possibilities deserve further investigation.

Repeat expansions interaction had become a focus in recent SCA research. We found that repeat expansion in *TBP*, which is associated with SCA17 at the full repeat expansions, can be a genetic modifier for dystonia in SCA1. This relation had not been found before, but SCA17 patients could have dystonia [2,37–39]. In two Brazilian SCA studies, they studied on the genetic modifier candidates, including repeat expansions of *ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7*, and *RAI1*, and they found there was no relationship between these genetic modifiers and dystonic phenotype in specific type of SCAs [6,11]. Our findings confirmed the Brazilian studies and we highlighted that interaction between repeat expansions could be an important genetic modifier for the clinical presentations of monogenetic, neurodegenerative disorders such as Huntington's disease and SCAs [10]. Particularly, genes of repeat expansions can interact with each other at the molecular level based on the SCA animal models and human pathology. For example, wild-type ataxin-2 can be recruited into the intranuclear aggregates formed at expanded ataxin-1 both in the SCA1 Drosophila model and SCA1 patient postmortem brain tissues [40]. In fact, ataxia-associated genes of repeat expansions have been identified to form complex protein interaction networks [41]. Although the *ATXN1* and *TBP* do not appear to be in the protein-protein interaction network [41], we could not rule out the possibility that these two genes could interact at the same molecular cascade. Further studies are required to elucidate the disease mechanism between *TBP* and SCA1. Nonetheless, the interactions between the protein products of the different repeat expansion genes could have synergistic effects, which preferentially affect different brain circuitries, leading to diverse clinical presentations. Therefore, the presence of dystonia as the results of these interactions can be an indicator of underlying pathology in the subgroups of each SCA, which might have the different rate of disease progression as is the case in SCA6. Studying the relationship between clinical features and genetic interactions in monogenetic disorders can help us better understand the disease pathomechanism.

Our study also found out that longer CAG repeat length was associated with faster ataxia progression in all SCAs. The relationship between progression rate and CAG repeat numbers were only established in SCA1 among EROSCA cohort [42], and different studies provided controversial results about this topic [42–45]. Future research of larger sample size is needed. In addition, when taking into different risk factors into account, the influence of CAG repeats and ataxia progressions among SCAs might differ [16–19].

Our study has several strengths. We studied the largest SCA cohort in the United States with the longitudinal follow-up that allows us to prospectively track disease progression. All the interviews and clinical examinations were performed by ataxia experts. Besides, we had detailed repeat expansion numbers in many genes for the analyses of genetic modifiers, which allowed us to study the gene-gene interactions.

There are several limitations in our study. First, we only recorded the dystonia at baseline; however, dystonia developed during the follow-up visit were not captured, which could change over time. Second, this study was focused on ataxia and conducted by ataxia experts with variable experience on the evaluation and treatment of dystonia, and a carefully standardized method for the ascertainment, evaluation and characterization of dystonia was not followed. Therefore, this study might suffer from low sensitivity on the detection of

dystonia and incomplete characterization. Besides, we did not systematically examine the sensory trick of dystonia as well as the writer's cramp and dystonia during spiral drawing. But our dystonia prevalence was still similar with the data of EUROSCA [34]. Third, the numbers of dystonic patient were relatively rare in SCA1 and SCA6, so our study should be considered as exploratory research, and a study of a larger sample size is needed in the future. Fourth, some subjects of present study had history of drug exposure, but we did not analyze the influences of the drug exposure on the presence of dystonia. Fifth, our groups had done serial studies in searching for the predictors for ataxia progression in CRC-SCA [16–19], and this is the fifth study. All of these studies were to analyze the existing data and the statistical analyses was not planned before the data collection. And the sample size was not large enough for us to take all the multiple variables into account into one analysis [16–19]. Nonetheless, our exploratory studies could still provide important insights into our understanding of SCAs.

In conclusion, the gene-gene interactions of different repeat expansion genes might affect the dystonia presentation in SCA1. Our study suggests that the presence of dystonia in patients of SCA6 might represent a subgroup, which has a slower disease progression. Future studies on the diverse clinical presentations and genetic influences in monogenetic disorders will further advance our understanding neurodegenerative disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2017.10.007.

Table 1

Baseline dystonia feature of 334 SCA participants.

Variables No. (%)	SCA 1 n = 58	SCA 2 n = 72	SCA 3 n = 134	SCA 6 n = 70	p-value[a]
Dystonia					**0.021**
Yes	7 (12.1)	13 (18.1)	33 (24.6)	6 (8.6)	
No	51 (87.9)	59 (81.9)	101 (75.4)	64 (91.4)	

Abbreviations: SCA = Spinocerebellar Ataxias. The value in bold represents statistical significance.

[a]Chi-square test.

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Table 2

Baseline features of 334 participants grouped by dystonia feature in the different subtypes of SCA.

	SCA 1 n = 58		p-value	SCA 2 n = 72		p-value	SCA 3 n = 134		p-value	SCA 6 n = 70		p-value
	Dystonia	**Non - Dystonia**		**Dystonia**	**Non - Dystonia**		**Dystonia**	**Non - Dystonia**		**Dystonia**	**Non - Dystonia**	
n (%)	7 (12.1)	51 (87.9)		13 (18.1)	59 (81.9)		33 (24.6)	101 (75.4)		6 (8.6)	64 (91.4)	
Age of onset (years)	43.57 ± 12.74	39.91 ± 11.39	0.440[b]	32.42 ± 10.77	37.40 ± 12.17	0.193[b]	31.06 ± 10.94	41.35 ± 11.11	**<0.001**[b]	46.33 ± 11.88	52.79 ± 10.14	0.147 [b]
Gender, M: W	4: 3	24: 21	1.000[a]	5: 7	36: 22	0.325[a]	17: 15	48: 48	0.759[a]	3: 3	34: 27	1.000 [a]
CAG repeat (numbers)	46.14 ± 6.84	45.88 ± 3.96	0.882[b]	40.15 ± 2.27 Median = 40.00	39.98 ± 3.41 Median = 39.00	0.464[c]	73.63 ± 4.54	70.04 ± 3.70	**<0.001**[b]	22.50 ± 0.55 Median = 22.50	22.35 ± 0.96 Median = 22.00	0.254 [c]
Disease duration (years)	11.00 ± 8.72	10.00 ± 7.03	0.736[b]	15.17 ± 7.15	14.54 ± 8.89	0.821[b]	14.31 ± 7.84	11.84 ± 7.36	0.109[b]	16.17 ± 13.57	13.18 ± 10.29	0.512 [b]

Abbreviations: SCA = Spinocerebellar Ataxia.

Values represent mean ± standard deviation or number, and for variables with non-normal distribution, the median is reported as well. The value in bold represents statistical significance.

[a] Chi-square test.

[b] 2 independent samples *t*-test.

[c] 2 independent samples Mann-Whitney *U* test.

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Table 3

Logistic regression analyses for the influencing genetic factors to the dystonia in SCAs.

Variables	Dependent variable: Dystonia											
	SCA1			SCA2			SCA3			SCA6		
	B	OR	p-value	B	OR	p-value	B	OR	p-value	B	OR	p-value
Age of first visit (years)	0.21	1.24	0.090	0.00	1.00	0.981	0.00	1.00	0.909	−0.05	0.95	0.339
Gender[a]	3.13	22.80	0.178	0.21	1.24	0.826	0.07	1.07	0.901	0.87	2.39	0.469
ATXN1 (SCA1) repeat numbers	0.44	1.55	0.127	−0.44	0.64	0.219	0.10	1.11	0.288	0.17	1.18	0.653
ATXN2 (SCA2) repeat numbers	−23.35	0.00	0.997	0.04	1.04	0.885	0.37	1.44	0.078	0.40	1.49	0.231
ATXN3 (SCA3) repeat numbers	0.08	1.08	0.710	0.25	1.29	0.110	0.30	1.35	**0.018**	0.11	1.12	0.585
CACNA1A (SCA6) repeat numbers	3.54	34.46	0.085	−0.45	0.64	0.218	0.09	1.09	0.709	0.25	1.28	0.634
ATXN7 (SCA7) repeat numbers	2.07	7.90	0.101	−0.47	0.63	0.352	−0.10	0.91	0.647	0.14	1.15	0.796
ATXN10 (SCA10) repeat numbers	0.17	1.19	0.489	−0.04	0.96	0.871	−0.20	0.82	0.366	−0.24	0.79	0.439
PP2R2B (SCA12) repeat numbers	−0.63	0.53	0.269	−0.25	0.78	0.176	−0.10	0.91	0.399	−0.04	0.96	0.806
TBP (SCA17) repeat numbers	−1.26	0.28	**0.040**	0.50	1.66	0.217	−0.14	0.87	0.449	−0.83	0.44	0.218
FRDA (FA) repeat numbers	0.37	1.45	0.072	−0.08	0.92	0.350	−0.06	0.95	0.442	−0.06	0.94	0.595

Abbreviations: FA = Friedreich's ataxia; OR = odds ratio. The value in bold represents statistical significance.

[a]Men = 0, Women = 1.

Table 4

Longitudinal SARA scores in GEE models.

Variables	Regression coefficients of SARA score[a]			
	SCA1	SCA2	SCA3	SCA6
Age of first visit (years)	0.53****	0.44****	0.60****	0.35****
Gender[b]	4.61**	−2.04	−0.30	−0.63
CAG repeat (numbers)	1.31****	1.99****	1.23****	2.11****
Dystonia[c]	7.48****	4.63**	9.08****	3.66
Visit time	0.72**	0.50	0.44***	1.63****
Dystonia × Visit time	1.31	−0.53	−0.08	−1.87*

Abbreviations: SARA = Scale for Assessment and Rating of Ataxia; GEE = Generalized Estimating Equation; SCA = Spinocerebellar ataxia.

* p< 0.05,

** p < 0.01,

*** p < 0.005,

**** p < 0.001.

[a] All regression coefficients and p-value were calculated in the GEE models, adjusting for age of first visit, gender, CAG repeat, dystonia and dystonia*visit time.

[b] Men = 0, Women = 1.

[c] Non-dystonia = 0, Dystonia = 1.