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The Initial Symptom and Motor Progression in Spinocerebellar Ataxias

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Dr. Lo: revision of the manuscript for important intellectual content.

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Abstract

Objective—To determine whether the initial symptom associates with motor progression in spinocerebellar ataxias (SCAs).

Background—SCAs are clinically heterogeneous and the initial presentation may represent different subtypes of SCA with different motor progression.

Methods—We studied 317 participants with SCA1, 2, 3, and 6 from the Clinical Research Consortium for SCAs (CRC-SCA) and repeatedly measured the severity of ataxia for 2.5 years. SCA patients were divided into gait-onset and non-gait-onset (speech, vision, and hand dexterity) groups based on the initial presentation. In addition to demographic comparison, we employed regression models to study ataxia progression in these two groups after adjusting for age, sex, and pathological CAG repeats.

Results—The majority of SCA patients had gait abnormality as an initial presentation. The pathological CAG repeat expansions were similar between the gait-onset and non-gait-onset groups. In SCA1, gait- onset group progressed slower than non-gait-onset group, while gait-onset SCA6 group progressed faster than their counterpart. In addition, the disease presented nine years later for SCA2 gait-onset group than non-gait-onset group. Initial symptoms of SCA3 did not influence age of onset or disease progression.

Conclusions—The initial symptom in each SCA has a different influence on age of onset and motor progression. Therefore, gait and non-gait-onset groups of SCAs might represent different subtypes of the diseases.

Keywords

spinocerebellar ataxias; subtypes; cerebellum; neurodegeneration

INTRODUCTION

Spinocerebellar ataxias (SCAs) are a genetically and clinically heterogeneous group of autosomal-dominant neurodegenerative disorders, characterized by various cerebellar features: gait difficulty, vision abnormalities, loss of limb dexterity, and speech disturbances [1]. SCA 1, 2, 3, and 6 account for the most common types of inherited ataxias and are caused by CAG repeat expansions within their respective genes [2]. The length of pathological CAG repeats is predictive of approximately 50-70% of age of onset [3-5], but there is still significant variability in age of onset and motor progression even among SCA patients with the same pathological CAG repeat numbers.

The initial clinical symptoms in neurodegenerative diseases may be of prognostic value. For example, Parkinson's disease (PD) can be divided into tremor dominant or postural instability and gait difficulty (PIGD) subtypes, with the tremor dominant PD subtype having an earlier age of onset, slower motor progression, and less cognitive impairment [6-10]. This concept of disease subtypes based on clinical presentations has not yet been applied to SCAs, and thus we studied whether the initial symptom would be predictive of ataxia progression in SCA1, 2, 3, and 6.

PATIENTS AND METHODS

Patient selection

The study subjects were evaluated by ataxia specialists during January 2010-August 2012 from 12 participating centers of the Clinical Research Consortium for SCAs (CRC-SCA) [11]. These SCA patients were either self-referred to specialty clinics or through 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. Our inclusion criteria were 1) the presence of ataxia, 2) definite genetic diagnosis of SCA1, 2, 3, or 6 either for the subject or another affected family member with ataxia, 3) willingness of participation, and 4) age of 6 years and older. The exclusion criteria were 1) known recessive, X-linked, and mitochondrial ataxias, 2) exclusion of SCA1, 2, 3, and 6 by genetic tests, 3) concomitant disorder(s) that affect ataxia measurements used in this study. Face-to-face interviews were done with each patient by ataxic specialists and the basic demographics and the presenting symptoms were recorded, including the initial ataxic symptoms: gait, speech, vision, and hand abnormalities. All participants were asked to provide blood samples for SCA genotyping. Subjects were followed every 6 months until 2 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) [11], evaluated the functional capacity using Unified Huntington's Disease Rating Scale part IV (UHDRS-IV) [12], scored the overall health status using EQ-5D [13], and assessed depressive symptoms by PHQ-9 questionnaire [14], which has been applied in SCA population [15-17].

Genetic Testing

DNA samples from blood of 213 participants were obtained and the CAG repeat expansions were determined in Dr. Stefan Pulst's laboratory (SCA1: 34, SCA2: 46, SCA3: 86, SCA6: 47). The Qiagen FlexiGene DNA Kit (Qiagen, Hilden, Germany) was used to extract DNA and CAG repeat expansions of SCAs were determined by multiplex polymerase chain reaction, followed by capillary electrophoresis with internal standards. Re-genotyping and Sanger sequencing were performed for verification of repeat length in 10% of all samples. For 86 patients whose blood samples were not available in the research lab, we used the repeat numbers from the commercial labs.

Predictor Variables

Ages of onset of any ataxic symptoms including gait abnormality, hand clumsiness, visual disturbances, and speech abnormality were collected. According to the reported age at symptom onset, each subject was then categorized into the gait-onset group if walking abnormality was the first symptom or one of the first symptoms exhibited, or the non-gait-onset group if the other three symptoms (hand, vision, and speech) occurred prior to the walking abnormality. The presence or absence of gait abnormality as a first manifestation of disease was used as a major predictor and was treated was a dichotomous variable.

Outcome Variables

SARA, our primary outcome, measured motor performance with a total score ranging from 0 to 40. Higher SARA scores reflected worse motor performance. UHDRS-IV was used to assess functional performance in daily activities through 25 questions. One point was given to each question with a “yes” reply, with the score ranging from 0 to 25. Higher UHDRS-IV scores indicated better functional performance. The EQ-5D used five areas including mobility, self-care, usual activities, pain/discomfort, anxiety/depression, to assess global health status with three rating levels (no problems = 0, some problems = 1, extreme problems = 2), ranging from 0 to 10 in total. The PHQ-9 used nine questions to assess depressive mood over the previous two weeks and four levels were scored (not at all = 0; several days = 1; more than half the days = 2; nearly every day = 3) for each question, ranging from 0 to 27 in total; higher scores reflected more severe depression. The above outcome measures were all treated as continuous variables.

Statistical Analysis

We first assessed whether each of basic demographics of SCAs is normally distributed using Kolmogorov–Smirnov test. For normally distributed variables, we used Student's t-test to compare gait-onset with non-gait-onset groups. For non-normally distributed variables, we used the Mann-Whitney U-test to compare gait-onset with non-gait-onset groups.

SCA1, 2, 3, and 6 were treated as four independent cohorts and analyzed separately. Chi-squared tests, two-independent samples t-tests, two-independent samples Mann-Whitney U tests were used to compare baseline demographics between the gait-onset vs. the non-gait-onset subgroups within each of the four SCA groups. We used repeated-measures linear regression (an exchangeable working within-subject correlation model by a generalized estimating equation [GEE]) to compute the average rates of disease progression in gait-onset

group and non-gait-onset group of each SCA type after controlling for age, sex, pathological CAG repeat number. SCA6 has been shown to have a non-linear disease progression [18], implying that the motor symptom progression might differ at different disease time points; therefore, we performed a secondary analysis to additionally adjust for the disease duration in SCA6.

The longitudinal patterns of ataxia progression of the two groups (gait-onset vs. non-gait-onset) during the two-year observation were assessed by entering the interaction terms (subtype × time) into the GEE models. Coefficients of the interaction terms reflected how the rate of motor progression differed by the presence of gait disturbance as the first manifestation of SCAs. All statistical analyses were performed using SPSS software (version 23).

RESULTS

A total of 317 SCA patients participated in the study (SCA1: 52, SCA2: 69, SCA3: 128, SCA6: 68). Gait abnormality presented as the first symptom in over 80% of the SCA patients (SCA1: 92.3%, SCA2: 87%, SCA3: 87.5%, SCA6: 83.8%, $p = 0.585$). The sex ratio, number of pathological CAG repeats, baseline SARA, UHDRS-IV, PHQ-9, and EQ-5D scores were similar between gait-onset group and non-gait-onset groups in each SCA cohort (Table 1). While the age of disease onset were comparable for gait-onset and non-gait-onset group of SCA1, SCA3, and SCA6 (SCA1: gait-onset 40.4 ± 11.6 vs. non-gait-onset 37.8 ± 14.6, $p = 0.671$; SCA3: gait-onset 38.0 ± 11.5 vs. non-gait-onset 37.8 ± 13.5, $p = 0.932$; SCA6: gait-onset 52.2 ± 9.8 vs. non-gait-onset 49.4 ± 14.2, $p = 0.554$), SCA2 gait-onset group developed disease nine years later than the non-gait-onset group (gait-onset 37.2 ± 11.4 vs. non-gait-onset 28.2 ±14.8, $p = 0.039$). The SCA3 non-gait-onset group had six year longer disease than their counterpart at the first visit (non-gait-onset 18.2 ± 9.5 vs. gait-onset 12.6 ± 7.4, $p = 0.019$).

In the linear regression models adjusting for age, sex, and pathological CAG repeat numbers, gait-onset group and non-gait-onset group had similar baseline SARA scores for all the SCA groups (SCA1: $\beta = -4.89$; SCA2: $\beta = -2.84$; SCA3: $\beta = 1.97$; SCA6: $\beta = -2.14$, all $p > 0.05$) (Table 2). Additionally, gait-onset group and non-gait-onset group in each SCA cohort did not differ in their baseline UHDRS-IV, PHQ-9 or EQ-5D scores (Table 2).

Gait-onset SCA1 patients had slower ataxia progression in SARA scores than non-gait-onset SCA1 patients ($\beta = -1.03$, $p = 0.005$). In SCA6 patients, the gait-onset group deteriorated faster than the non-gait-onset group ($\beta = 1.60$, $p < 0.001$) (Table 3). In our secondary analyses adjusting for disease duration, the gait-onset SCA6 patients still had faster motor progression than non-gait-onset SCA6 patients (SARA: $\beta = 1.70$, $p < 0.001$). In SCA2, gait-onset group had slower progression of UHDRS-IV scores compared to non-gait-onset group ($\beta = -0.83$, $p = 0.036$). In SCA3, gait-onset group and non-gait-onset group did not different in the rate of ataxia progression. Otherwise, we did not observe any differences in the progression of UHDRS-IV, ED-5D, or PHQ-9 between gait-onset group and non-gait-onset

groups in SCAs (Table 3). These outcome variables of the last visit were also listed as the Supplemental table 1.

Among the non-gait-onset symptoms, visual disturbance as the initial symptom was particularly common in SCA3 and SCA6 (2 SCA1 (3.8%), 1 SCA2 (1.4%), 14 SCA3 (10.9%), 7 SCA6 (10.3%)).

DISCUSSION

Walking problem presented as the initial symptom in over 80% of our patients with SCAs, more often than an earlier study by Globas et al [19]. Interestingly, gait-onset SCA patients differed in age of onset and motor progression. Gait abnormality as an initial motor symptom is associated with a slower progression in SCA1, a later age of onset in SCA2, and a faster progression in SCA6; however the motor associations did not extend to non-motor symptoms of SCAs such as depression. Functional status measured by UHDRS-IV (except SCA2) or quality of life measured by EQ-5D was not associated with gait abnormality as the initial symptom either. SCA2 patients commonly have postural and action tremors in the upper extremities which may cause severe functional impairment leading to lower UHDRS-IV scores [20, 21]. It is possible that SCA2 patients with initial symptoms of upper limb tremor may be more functionally disabled in their daily activities than SCA2 patients with initial symptoms of gait difficulty. These possibilities deserve further investigation.

The initial symptoms of SCAs are of prognostic value in predicting distinct disease courses. Our findings highlight the importance of studying the heterogeneity of SCAs since the initial symptoms of SCAs might represent different subtypes with distinct prognoses. Each of the SCAs likely shows different neurodegeneration patterns initially which extends to more widespread regions of the brain as the disease progresses [22, 23]. This concept has been applied to other neurodegenerative disorders such as PD. In PD, the tremor dominant subtype has slower motor progression and a lower risk of dementia than those with PIGD subtype [6-10]. In addition, tremor dominant PD has less gray matter atrophy and more functional connectivity when compared to PIGD dominant PD [24], suggesting that clinical subtypes might reflect the underlying different neuropathological substrates. In a similar fashion, our findings that gait- and non-gait-onset SCA subtypes correlate differently with age of disease onset and motor progression support the idea of the heterogeneity of SCA pathology [22]. For example, non-gait-onset SCA2 subtype having an earlier disease when compared its gait-onset subtype may reflect earlier disease pathology in the visual/oculomotor and speech centers of the brain [22, 23]. Interestingly, initial symptoms in SCA3 do not affect age of onset or disease progression, which may be attributed to its distinct pathology with relative preservation of Purkinje cells and cerebellar cortex when compared to the other three SCA types [22]. These possibilities of distinct patterns of progression in ataxia subtypes also should be probed further.

SCA patients can have very diverse clinical presentation in addition to ataxia; therefore, the initial symptoms can vary in different SCAs. SCA1 patients often show pancerebellar ataxia, lower extremity spasticity, oculomotor signs, extrapyramidal syndrome in the later stage of disease course, and polyneuropathy in cases with a high CAG repeat numbers [20, 21].

SCA2 patients can have slow saccades, postural and action tremor, polyneuropathy, upper motor neuron signs, and parkinsonism, which could be a predominant feature in some cases. SCA2 cases with longer CAG repeats also often have myoclonus, dystonia, and myokymia [20, 21, 25]. SCA3 patients can have spasticity and oculomotor abnormality and SCA3 can be further divided into 5 subtypes. Type 1 SCA3 patients have early onset ataxia with marked pyramidal signs along with dystonia, proptosis, and facial and lingual fasciculations. Type 2 SCA3 patients have intermediate age of onset of ataxia and commonly have polyneuropathy. Type 3 SCA3 patients have late onset of ataxia and have prominent spasticity, polyneuropathy, and ophthalmoplegia. Type 4 SCA3 patients have predominant levodopa-responsive parkinsonism, polyneuropathy, and fasciculations. Type 5 SCA3 patients have spastic paraparesis [26]. SCA6 patients have relatively pure cerebellar ataxia syndrome [20, 21]. Clinical presentations of SCAs are closely linked to the size of CAG repeats. For example, a larger repeat size in SCA1 is associated with motor neuron signs [21] and SCA3 subtypes are also largely determined by the repeat size as well [26]. Interestingly, we did not find any differences in the CAG repeat numbers between gait-onset and non-gait-onset cases in each SCA (Table 1), showing that CAG repeat numbers do not play a major role in determining the initial presentations of SCAs.

Interestingly, we found that visual disturbances as the initial symptom is common in SCA3 cases, consistent with a previous report [19]. Our study also showed SCA6 patients also commonly have visual disturbance at the disease onset. Thus, clinicians should consider these two genetic forms for ataxia when encountering ataxia with vision problems as the initial symptom.

One of the major limitations is that we did not have information on the specific etiology leading to classification within the four broad initial symptom categories. Gait abnormalities in SCAs are heterogeneous in phenotype and may reflect various etiologies, including the wide-based gait due to ataxia or the slow and shuffling gait of parkinsonism or the stomping gait from peripheral neuropathy. Vision problems may be due to diplopia or reduced visual acuity which can be embedded within the four types of SCAs studied. Our study did not directly address the specific types of symptoms leading to visual disturbance or gait abnormality, and better characterization of initial symptoms could potentially lead to a better predictive value for ataxia progression. Furthermore, since approximately 8-18 years lapsed between the onset of the diseases and the first visit, it is difficult to know the exact nature of the initial symptoms and their precise timeline. Also, the two-year observation period may not be long enough to fully examine the progression of SCAs. Finally, non-motor features of SCAs also progress over time [18], and the initial symptoms could affect the progression rate of non-motor features; however, non-motor features were not measured longitudinally in the current study. Our study has several strengths. First, this is a large, multi-center, prospective study that characterizes the motor and non-motor progression of SCA1, 2, 3, and 6 in North America. Second, we used standardized and validated rating scales to assess both motor features (SARA) and non-motor features (PHQ-9, UHDRS-IV and EQ-5D) [11-14] making our study results more likely comparable. Third, both pathological CAG repeat number and disease duration, two major factors impacting disease progression in SCAs, were accounted for in this study [3-5].

In conclusion, our study indicated that the initial symptom of SCAs is closely associated with the age of onset and motor progression. In agreement with previous studies, the majority of SCA patients had gait abnormality as an initial presentation. Additionally, gait abnormality as an initial motor symptom is associated with a slower progression in SCA1, a later age of onset in SCA2, and a faster progression in SCA6. Gait- and non-gait onset groups within each SCA may represent different subtypes of SCAs and may reflect distinct underlying pathology. Future studies should focus on the detailed characterization of the initial symptoms in a larger sample size with longer follow-up to further strengthen our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline features of 317 participants in the CRC-SCA cohort.

	SCA 1		*p*-value	SCA 2		*p*-value	SCA 3		*p*-value	SCA 6		*p*-value
	Gait-onset	**Non-gait-onset**		**Gait-onset**	**Non-gait-onset**		**Gait-onset**	**Non-gait-onset**		**Gait-onset**	**Non-gait-onset**	
n (%)	48 (92.3)	4 (7.7)		60 (87.0)	9 (13.0)		112 (87.5)	16 (12.5)		57 (83.8)	11 (16.2)	0.585[a]
Age at first visit (yrs)	50.9 ± 12.9	46.3 ± 15.7	0.493[b]	52.4 ± 12.2	42.9 ± 17.3	0.144[b]	50.6 ± 12.3	55.9 ± 11.8	0.105[b]	66.5 ± 9.7	60.2 ± 14.5	0.190[b]
Age of onset (yrs)	40.4 ± 11.6	37.8 ± 14.6	0.671[b]	37.2 ± 11.4	28.2 ± 14.8	**0.039[b]**	38.0 ± 11.5	37.8 ± 13.5	0.932[b]	52.2 ± 9.8 Median = 52.0	49.4 ± 14.2 Median = 48.0	0.554[c]
Disease duration (yrs)	10.6 ± 7.2 Median = 8.0	8.5 ± 7.9 Median = 6.0	0.324[c]	15.3 ± 8.6 Median = 14.0	14.7 ± 9.3 Median = 14.0	0.789[c]	12.6 ± 7.4 Median = 12.0	18.2 ± 9.5 Median = 19.5	**0.019[c]**	14.4 ± 11.0 Median = 11.0	10.8 ± 4.9 Median = 9.0	0.605[c]
Sex, M:W	28:20	1:3	0.310[a]	32:28	7:2	0.281[a]	56:56	10:6	0.428[a]	30:27	8:3	0.323[a]
CAG repeat	46.0 ± 4.6	48.0 ± 2.5	0.391[b]	39.4 ± 2.5 Median = 39.0	39.6 ± 7.6 Median = 40.0	0.243[c]	71.0 ± 4.0 Median = 71.0	70.3 ± 4.1 Median = 71.0	0.432[c]	22.3 ± 0.8 Median = 22.0	22.5 ± 1.6 Median = 22.0	0.626[c]
Baseline SARA score	14.1 ± 8.3	19.6 ± 6.8	0.198[b]	16.7 ± 7.6	16.8 ± 6.1	0.965[b]	15.2 ± 9.2 Median = 14.0	14.8 ± 6.9 Median = 14.5	0.925[c]	13.9 ± 7.3	15.0 ± 8.5	0.674[b]
Baseline UHDRS-IV score	18.9 ± 6.4 Median = 20.0	15.0 ± 4.8 Median = 15.0	0.149[c]	18.5 ± 6.2 Median = 20.0	19.0 ± 5.0 Median = 19.0	0.978[c]	17.2 ± 7.0 Median = 18.0	17.0 ± 6.3 Median = 19.0	0.694[c]	18.6 ± 5.8 Median = 20.0	18.6 ± 5.9 Median = 21.0	0.861[c]
Baseline PHQ-9 score	5.7 ± 6.4 Median = 3.0	13.0 ± 8.7 Median = 12.5	0.050[c]	5.4 ± 5.6 Median = 3.5	4.1 ± 3.7 Median = 3.0	0.838[c]	7.5 ± 6.0 Median = 6.0	6.1 ± 3.6 Median = 5.5	0.573[c]	6.6 ± 6.0 Median = 5.0	5.6 ± 5.8 Median = 5.0	0.627[c]
Baseline EQ-5D score	3.0 ± 1.7 Median = 5.0	4.8 ± 1.5 Median = 3.0	0.065[c]	3.1 ± 1.7 Median = 3.0	2.0 ± 1.2 Median = 2.0	0.064[c]	3.5 ± 2.1 Median = 3.0	3.8 ± 1.4 Median = 4.0	0.358[c]	3.1 ± 1.7 Median = 3.0	2.6 ± 1.8 Median = 2.5	0.429[c]

Abbreviations: CRC-SCA = the Clinical Research Consortium for Spinocerebellar Ataxias; SARA = Scale for Assessment and Rating of Ataxia; UHDRS = Unified Huntington's Disease Rating Scale; PHQ-9 = Patient Health Questionnaire; EQ-5D = quality of life measurement from 5 domains.

Values represent mean ± standard deviation or number, and for variables with non-normal distribution, the median is reported as well.

Values in bold are statistically significant.

[a] Chi-square test

[b] Two-independent samples t-test

[c] Two-independent samples Mann-Whitney U test

Table 2

Baseline SARA, UHDRS-IV, PHQ-9, and EQ-5D scores in gait and non-gait-onset groups.

	Regression coefficients of baseline SARA score[a]			
	SCA1	**SCA2**	**SCA3**	**SCA6**
Age of first visit (yrs)	0.24	0.31***	0.54****	0.35****
Sex[b]	2.08	−1.25	−0.10	0.29
CAG repeat	0.44	1.00***	1.30****	1.95*
Initial symptom[c]	−4.89	−2.84	1.97	−2.14

	Regression coefficients of baseline UHDRS-IV score[a]			
	SCA1	**SCA2**	**SCA3**	**SCA6**
Age of first visit (yrs)	−0.18	−0.14	−0.39****	−0.32****
Sex[b]	−1.76	0.63	−0.12	0.74
CAG repeat	−0.33	−0.47	−1.16****	−1.64*
Initial symptom[c]	3.34	1.09	−0.80	2.01

	Regression coefficients of baseline PHQ-9 score[a]			
	SCA1	**SCA2**	**SCA3**	**SCA6**
Age of first visit (yrs)	0.07	0.01	0.17**	−0.12
Sex[b]	−0.35	−0.54	1.19	−1.17
CAG repeat	0.22	0.01	0.25	−1.36
Initial symptom[c]	−7.18	1.00	2.01	1.56

	Regression coefficients of baseline EQ-5D score[a]			
	SCA1	**SCA2**	**SCA3**	**SCA6**
Age of first visit (yrs)	0.04	0.04	0.09****	0.00
Sex[b]	−0.05	−0.15	0.05	−0.27
CAG repeat	0.12	0.10	0.22***	−0.20
Initial symptom[c]	−1.69	0.60	−0.08	0.22

Abbreviations: SARA = Scale for Assessment and Rating of Ataxia; UHDRS = Unified Huntington's Disease Rating Scale; PHQ-9 = Patient Health Questionnaire; EQ-5D = quality of life measurement from 5 domains; SCA = Spinocerebellar Ataxia.

[a] All regression coefficients were calculated in linear regression model, adjusting for age of first visit, sex, CAG repeat and initial symptom.

[b] Man = 0, Woman = 1

[c] Non-gait-onset = 0, Gait-onset = 1

* $p < 0.05$

** $p < 0.01$

*** $p < 0.005$

**** $p < 0.001$

Table 3

Longitudinal SARA, UHDRS-IV, PHQ-9, and EQ-5D scores of gait and non-gait-onset groups in GEE model.

	Regression coefficients of SARA score[a]			
	SCA1	**SCA2**	**SCA3**	**SCA6**
Age of first visit (yrs)	0.26	0.30****	0.55****	0.35****
Sex[b]	2.99	−1.68	−0.19	−0.14
CAG repeat	0.56	0.89*	1.30****	2.24****
Initial symptom[c]	−5.33	−2.03	2.20	−3.50
Visit time	2.11****	0.70	0.37	−0.00
Initial symptom × Visit time	−1.03**	0.03	−0.02	1.60****

	Regression coefficients UHDRS-IV score[a]			
	SCA1	**SCA2**	**SCA3**	**SCA6**
Age of first visit (yrs)	−0.17	−0.14*	−0.55****	−0.23***
Sex[b]	−2.41	0.31	0.08	0.15
CAG repeat	−0.34	−0.59	−1.36****	−1.43
Initial symptom[c]	3.14	1.27	−1.27	1.52
Visit time	−0.68	0.96***	−0.60	−0.21**
Initial symptom X Visit time	0.12	−0.83*	−0.57	−0.36

	Regression coefficients of PHQ-9 score[a]			
	SCA1	**SCA2**	**SCA3**	**SCA6**
Age of first visit (yrs)	0.04	0.00	0.18*	−0.05
Sex[b]	−0.05	−1.41	1.91	−0.88
CAG repeat	0.19	−0.07	0.35	−0.87
Initial symptom[c]	−8.35*	2.63	1.52	0.51
Visit time	−1.07	2.06	0.64	−0.80
Initial symptom X Visit time	1.18	−1.81	−0.05	0.75

	Regression coefficients of EQ-5D score[a]			
	SCA1	**SCA2**	**SCA3**	**SCA6**
Age of first visit (yrs)	0.04	0.03*	0.08****	−0.03
Sex[b]	−0.13	−0.30	0.04	0.23
CAG repeat	0.13	0.11	0.20***	−0.10

	Regression coefficients of EQ-5D score[a]			
	SCA1	**SCA2**	**SCA3**	**SCA6**
Initial symptom[c]	−1.64*	0.54	−0.20	0.32
Visit time	−0.17	−0.33	−0.03	−0.04
Initial symptom X Visit time	0.29	0.22	0.25	0.19

Abbreviations: SARA = Scale for Assessment and Rating of Ataxia; UHDRS = Unified Huntington's Disease Rating Scale; PHQ-9 = Patient Health Questionnaire; EQ-5D = quality of life measurement from 5 domains; GEE = Generalized Estimating Equation; SCA = Spinocerebellar Ataxia.

[a] All regression coefficients were calculated in GEE model, adjusting for age of first visit, sex, CAG repeat, initial symptom, and initial symptom*visit time.

[b] Man = 0, Woman = 1

[c] Non-gait-onset = 0, Gait-onset = 1

* <0.05

** <0.01

*** <0.005

**** <0.001