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ORIGINAL PAPER

The Responsiveness of Triaxial Accelerometer Measurement of Gait Ataxia Is Higher than That of the Scale for the Assessment and Rating of Ataxia in the Early Stages of Spinocerebellar Degeneration

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Abstract

We reported previously that the average medial–lateral gait amplitude while walking on a straight path determined using triaxial accelerometers fixed on the middle of the upper back may be a quantitative and concise indicator for the severity of cerebellar ataxia. Considering that gait ataxia is a typical initial symptom in a variety of spinocerebellar degeneration (SCD), we aimed to develop quantitative biomarkers for cerebellar ataxia as metric variables. We used triaxial accelerometers to analyze gait parameters in 14 patients with SCD at 3 points over 3 years (at baseline, 1.5 years and 3 years). Analysis of covariance (ANCOVA) models adjusted for the baseline scores were used to estimate sample sizes. The mean medial–lateral amplitude (ML) gained by a triaxial accelerometer fixed on upper back could detect the each 1.5-year change. In the 14 patients, the mean ML(m) was 0.032 ± 0.007(SD) at entry, 0.037 ± 0.008 after 1.5-year follow, and 0.042 ± 0.020 after 3-year follow. In contrast, SARA gait scores were 2.9, 2.9, and 3.0, respectively. The responsiveness of the quantitative evaluation of *gait ataxia* by triaxial accelerometers is higher than that of the SARA within a 1.5-year follow-up period. Gait analysis by triaxial accelerometers will be complementary to the evaluation of scales like SARA in the assessment of clinical severity of SCD patients in early stage.

Keywords Cerebellar ataxia · Quantitative evaluation · Accelerometer · Biomarker

Introduction

The clinical severity of cerebellar ataxia is often determined in accordance with rating scales based on clinical symptoms and the activities of daily life (ADL). The Scale for the Assessment and Rating of Ataxia (SARA) is used to assess the severity of ataxia [1, 2], and the Berg Balance Scale (BBS) is used to determine balance in patients [3, 4]. Because these scales, however, are not metric variables but are expressed as category characteristics, it is critically essential to develop biophysiological biomarkers that appropriately reflect equilibrium function of patients with ataxia with spinocerebellar degeneration (SCD) so that disturbances in postural control of these patients could be quantitively evaluated.

It is well recognized that the cerebellum regulates postural equilibrium and muscle tone by acting on the brainstem and cerebral cortex [5, 6]. Specifically, fastigial efferents on the vestibular nuclei and reticular formation are likely involved in balance control, muscle tone regulation, and locomotion [7, 8]. Moreover, cerebellar output reaches vast areas of the cerebral cortex, including the prefrontal and posterior parietal cortices, in addition to motor-related areas [9]. The cerebellum may contribute to the cognitive aspects of postural control such as maintenance of postural verticality [10] and anticipatory postural adjustment [11] via connections with the cerebral cortex. Because the cerebellum achieves the above processes of controlling posture depending on real-time sensory information in visual, vestibular, and proprioceptive signals, we hypothesize that equilibrium disturbances in patients with

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SCD can be more sensitively detected during ongoing movements than quiet standing. To verify the above hypothesis, so far, attempts have been made to evaluate postural control capability using stabilometers [12] and triaxial accelerometers [13] in patients with SCD. We found that postural instability measurements by triaxial accelerometers were well correlated with severity of ataxia in patients with SCD during walking [13], while those by stabilometers during quiet standing had no correlation [14]. Particularly, the mean amplitude of acceleration in the medial–lateral direction (ML amplitude), which was measured by triaxial accelerometers attached at the upper back of the patients, during walking on a straight path was well correlated with SARA scores [13], increasing the possibility that the ML amplitude is a clinically useful physiological biomarker in patients with SCD. In contrast, the majority of the published studies on inertial sensors generally used a root mean square (RMS) of acceleration along each of the three axes as a measurable parameter [14, 15].

Accordingly, the present study was designed to verify which physiological biomarkers, the ML amplitude or RMS, is more superior in reflecting SCD severity. Because SARA is more generally utilized for the evaluation of cerebellar ataxia than BBS, we compared which biomarkers had higher correlation with SARA scores in patients with SCD. In the current study, changes in postural control in patients with SCD were investigated for more than 3 years, i.e., at the initial assessment, 1.5 years, and 3.0 years in the quiet standing conditions with open-closed eyes and walking on a straight path for 6 min. Then, the mean ML amplitude and RMS of the triaxial accelerations were calculated. The present findings suggest that ML amplitude had higher correlation with the SARA score than RMS and exhibited more sensibility in detecting initial signs of posture-gait deficiency in patients with SCD than the SARA score, indicating that the mean ML amplitude can be a more critical parameter in planning clinical therapeutic studies.

Subjects and Methods

Subjects

First, we analyzed 25 patients with SCD whose data had been evaluated in a previous study [13]. The RMS of acceleration was measured by triaxial accelerometers. Next, we analyzed 14 patients with degenerative ataxia from January 2015 to October 2016 (Table 1): 7 patients with spinocerebellar ataxia type 6 (SCA6), 2 patients with SCA31, 2 patients with dominantly inherited cortical cerebellar atrophy (DCCA) whose SCA genotype was still not determined, and 3 patients with sporadic cortical cerebellar atrophy (CCA). There were 7 male and 7 female subjects with an average age of 65.7 ± 9.4 years (range, 48–84 years). We evaluated the clinical severity of each patient using SARA and BBS. Gait and clinical symptoms were evaluated in all patients from June 2013 to August 2014. At that time, we assessed 25 patients with degenerative ataxia. Since then, 11 patients had dropped out from this study

Table 1 Clinical profiles of patients in the 3-year follow-up study

No. of patient	Diagnosis	Sex	Age at onset (years)	Age at the last evaluation of the 3-year follow-up	Disease duration between onset and last examination
1	SCA6	M	55	68	13
2	Sporadic CCA	F	72	76	4
3	Dominant CCA	F	47	56	9
4	SCA6	F	56	67	11
5	SCA6	F	62	84	22
6	SCA6	M	43	66	23
7	SCA31	M	60	77	17
8	SCA6	F	51	62	11
9	Dominant CCA	M	46	57	11
10	Sporadic CCA	M	62	69	7
11	Sporadic CCA	M	36	48	12
12	SCA6	F	46	58	12
13	SCA6	F	62	66	4
14	SCA31	M	58	66	8
Mean				65.7	11.7
SD				9.4	5.7

SCA spinocerebellar ataxia, *CCA* cortical cerebellar atrophy,*SD* standard deviation

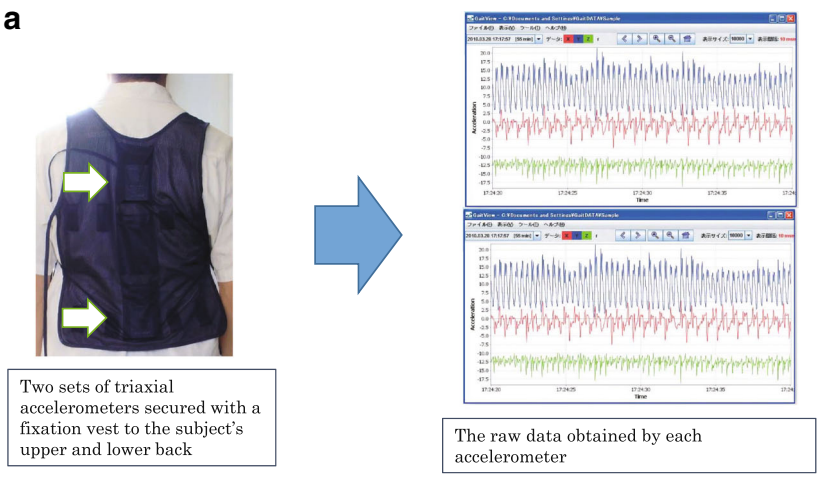

Fig. 1 Quantitative analysis by triaxial accelerometers. **a** Position of triaxial accelerometers. Left: Two sets of triaxial accelerometers (arrows) secured with a fixation vest to the subject's lower and upper back measured acceleration signals. Right: Raw output of acceleration data from the upper and lower sensors (red for the *x*-axis, blue for the *y*-axis, and light green for the *z*-axis). **b** Method of data analysis. When in the standing position, the subjects were evaluated with their eyes open for 1 min and then closed for another 1 min. When standing in the anatomical position, the orientations of the three acceleration axes, *X*, *Y*, and *Z*, were medial–lateral (ML), vertical (VT), and anterior/posterior (AP), respectively. **c)** Shuttle walk on a 30-m straight line for 6 min. The subjects were evaluated, while they shuttle walked on a 30 m straight line for 6 min. The amplitude time series was defined as (Y1 − Y2)/2 and divided into two parts: signals corresponding to straight walking and turning around the cone. The average and coefficient of variation (CV) of the amplitude time series were calculated separately for each part, which yielded the desired gait parameters

because they were unable to safely walk alone for 6 min. Each patient was evaluated three times, consisting of the initial evaluation (baseline) and 1.5-year intervals.

This clinical study was approved by the ethics panels of Hokkaido University Hospital and Kushiro Rosai Hospital.

Quantitative Assessment by Triaxial Accelerometers

Acceleration signals were measured during 6-min walking and 1-min standing tasks, using two sets of triaxial accelerometers (size, 7.5 cm × 5 cm × 2 cm; weight, 95 g; Mimamori-Gait™ System; LSI Medience, Tokyo, Japan) that were secured with a fixation vest to the middle of the subject's lower and upper back (Fig. 1a). The subjects were evaluated while they shuttle walked on a 30-m straight line for 6 min (6-min walk test [6MWT] [16]). Similar tasks were performed in the Japan SBMA Interventional Trial for TAP-144-SR (JASMITT) study and other studies [17]. Initially, the subjects were evaluated in the standing position with their eyes open for 1 min and then closed for an additional 1 min. An assistant remained beside the subject to prevent falls (Fig. 1b). Next, the subjects were evaluated while they shuttle walked on a 30-m straight line for 6 min (6MWT). When standing in an anatomical position, the orientations of the three acceleration axes—X, Y, and Z—were ML, vertical (VT), and anterior–posterior (AP), respectively. Data were collected at a sampling frequency of 100 Hz and stored on a secure digital memory card inserted into the device for later analysis. We extracted two gait parameters, the average and coefficient of variation (CV) of motion trajectory amplitude, from each acceleration component and divided them into walking on a straight path and turning, as described in our previous study (Fig. 1c) [13]: (1) The acceleration signal was integrated twice in the time domain and then high-pass filtered on a moving-window average to generate motion trajectory, i.e., relative displacement. (2) The upper and lower envelopes of the trajectory signal (Y1 and Y2) were determined by spline interpolation of its positive and negative peaks, respectively. (3) The amplitude time series was defined as (Y1 − Y2)/2 and divided into signals corresponding to walking on a straight path and turning. (4) The amplitude time series average and CV were calculated separately for each part to yield the desired gait parameters. To quantify body motion during standing, we examined the parameters as follows: (1) A moving-window average with a window size of 5.6 s was used to smoothen the three acceleration components, ax(t), ay(t), and az(t), to generate 3 baseline signals: Bx(t), By(t), and Bz(t). (2) Three parameters were calculated, max[|Bx(t) − Bx(0)|] (maximum drift along ML), max[|Bz(t) − Bz(0)|] (maximum drift along AP), and $\max[\{[Bx(t) - Bx(0)]^2 + [By(t) - By(0)]^2 + [Bz(t) - Bz(0)]^2\}^{0.5}]$ (maximum total drift), to quantify slow body movement-induced baseline drift. (3) Two parameters to quantify rapid body movement-induced fluctuations were determined using the standard deviation (SD) of ax(t) − Bx(t)

Table 2 Rating scores of SARA and Berg Balance Scale at baseline (1st), 1.5 years (2nd) and 3 years (3rd)

	Total SARA score			SARA gait sub score			SARA standing sub score			SARA limb subscore			Berg Balance Scale		
No. of patient	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd
1	7.5	11.5	7	2	3	2	1	2	1	3.5	3.5	2	52	48	52
2	3	10	8.5	1	2	2	0	1	1	2	5	4.5	53	49	52
3	8.5	9	9.5	2	2	2	2	1	1	2.5	3	3.5	56	52	53
4	12.5	15	11.5	4	3	3	2	2	2	5.5	6	4.5	47	49	51
5	10	13	15.5	3	3	4	2	2	2	4	4	6.5	43	40	43
6	8	7	14	2	3	3	2	1	2	3	2	5	49	50	46
7	16	19	19	4	4	4	3	2	3	6	8	8	38	35	27
8	9.5	13	17	2	3	3	2	1	2	5.5	7	9	60	50	41
9	11	10.5	11	3	3	2	1	2	1	5	4.5	6	52	50	41
10	6.5	15	16	2	3	3	1	2	3	3.5	6	6	49	43	37
11	11	14	15.5	3	3	3	2	2	2	6	6	7.5	47	49	46
12	13.5	17	19	4	4	4	2	2	2	5.5	6	8	41	40	33
13	12.5	7	11	4	2	3	2	1	2	3.5	3	5	41	38	40
14	12	14.5	16.5	3	3	4	1	1	2	5	6.5	6.5	45	50	47
Mean	10.1	12.5	13.6	2.9	2.9	3.0	1.6	1.6	1.9	4.3	5.0	5.9	48.1	45.9	43.5
SD	3.3	3.6	3.9	0.9	0.6	0.8	0.7	0.5	0.7	1.3	1.7	1.9	6.2	5.5	7.7

Scale for the Assessment and Rating of Ataxia (SARA), with gait, standing, and limb scores, Berg Balance Scale (BBS), gait distance, total baseline drift, and mean medial–lateral (ML) amplitude measured in the upper back of the 1st, 2nd, and 3rd assessment. SARA limb score consisted of finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide. Abbreviations are the same as those in Table 1

Table 3 Comparison of root mean square and 2-time integration value

	Root mean square (RMS)												2-time integration value		
Task and sensor position	Straight gait with lower back			Turning with lower back			Straight gait with upper back			Turning with upper back			Straight gait with upper back		
Direction	ML	VT	AP	ML	VT	AP	ML	VT	AP	ML	VT	AP	ML	VT	
Mean	0.156	1.032	0.215	0.154	1.030	0.212	0.165	1.019	0.212	0.165	1.019	0.213	0.039	0.013	
SD	0.043	0.018	0.062	0.042	0.021	0.065	0.044	0.028	0.083	0.041	0.030	0.084	0.014	0.005	
Correlation with SARA															
R	0.38	− 0.36	− 0.19	0.36	− 0.47	− 0.22	0.18	− 0.50	0.34	0.18	− 0.52	0.37	0.65	− 0.36	
p value	0.0601	0.0772	0.3509	0.0742	0.0180	0.3012	0.3843	0.0116	0.0951	0.3814	0.0071	0.0706	0.0004*	0.0759	
Correlation with gait distance															
R	− 0.09	0.73	0.47	− 0.10	0.82	0.50	− 0.03	0.62	− 0.15	− 0.05	0.68	− 0.20	− 0.78	0.87	
p value	0.6641	< 0.0001*	0.0177	0.6348	< 0.0001*	0.0104	0.8756	0.001	0.4729	0.7957	0.0002*	0.3437	< 0.0001*	< 0.0001*	

Root mean square (RMS) along each of the 3 axes of the initial 25 patients with SCA. They were evaluated by dividing them into 2 parts: straight gait and turning. *p value < 0.05 with the test for multiple comparison using the Holm–Bonferroni method

ML medial–lateral, *VT* vertical, *AP* anterior–posterior, *SD* standard deviation, *R* correlation coefficient

(fluctuation along ML) and az(t) − Bz(t) (fluctuation along AP). In our previous study with healthy controls, we reported that the CV of ML and VT amplitudes was significantly lower in the upper back than in the lower back, while the CV of AP was significantly decreased in the lower back compared with the upper back [13]. An increase in CV indicates that each stroke of gait differed (i.e., gait dysregulation). In the gait analysis, we used an upper back accelerometer for ML and VT amplitudes and a lower back accelerometer for AP amplitude. Then, we compared these data with the RMS along the three axes by evaluating its correlation with the SARA score and walking distance of 6MWT.

Sample Size Estimation

In order to assess responsiveness, analysis of covariance (ANCOVA) models adjusted for the baseline scores were used to estimate sample sizes using two-tailed tests and an α level of 0.05. The following formula was used to calculate sample size: $n = 2\sigma^2 / \delta^2[1-\rho^2] \times (z(\alpha/2) + z(\beta))^2$, where σ was the SD, δ was the absolute difference observed between two visits, ρ was the correlation between two visits, and $z(\alpha/2)$ and $z(\beta)$ were the z-scores of the standard normal distribution related to the size and power of the test, respectively [18].

Statistical Analysis

Data analyses were performed using the JMP® Pro 14.0.0 statistical software program (SAS Institute, Inc., Cary, NC, USA). We used Pearson's correlation coefficients for disease severity and analysis of each parameter. A test for multiple comparisons was conducted using the Holm–Bonferroni method. A p value < 0.05 was considered statistically significant. ANCOVA was performed with the total ΔML amplitude in the 3-year follow-up as a dependent variable and sex, age at onset, disease duration, and ML amplitude at baseline as independent variables. The test results were considered significant at an α level of 0.05 for this multivariate analysis.

Results

The SARA and BBS scores of the 14 patients in three consecutive years are shown in Table 2. Total SARA scores significantly correlated with the VT RMS from both the upper and lower back during turning and VT RMS from the lower back in a straight gait. Among these, the VT RMS from the upper back during turning had the strongest correlation to the total SARA score ($R = -0.52$, $p = 0.0071$), which was not significant by multiple comparison and less than the mean ML amplitude of the upper back during straight gait ($R = 0.65$, $p = 0.0004$) (Table 3 and Fig. 2). In contrast, both RMS of VT and

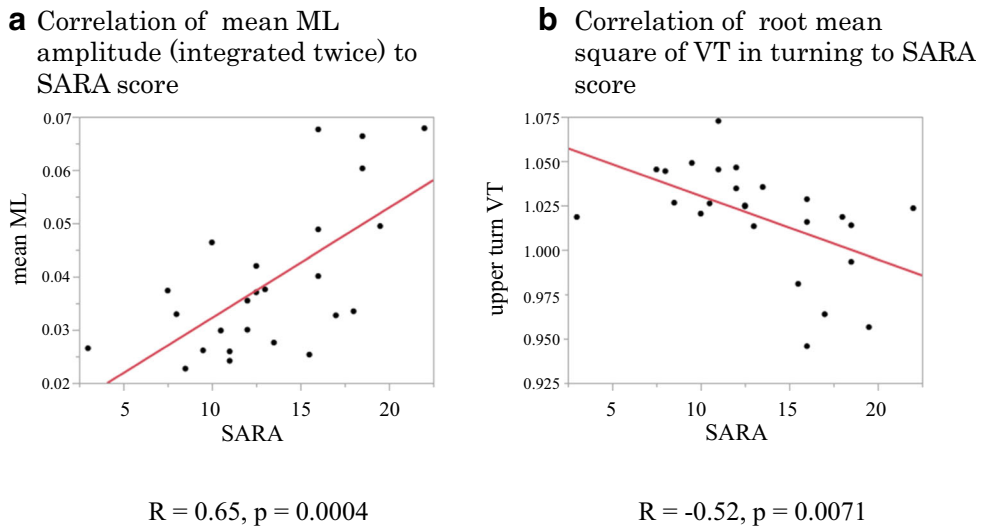

Fig. 2 Correlation of mean ML and RMS of VT with SARA score. **a** The mean ML amplitude of the upper back during straight gait correlated to total SARA score significantly by Holm's correlation ($R = 0.65$, $p = 0.0004$). **b** RMS evaluation showed that VT RMS from the upper back during turning had the strongest correlation to the total SARA score ($R = -0.52$, $p = 0.0071$). However, it was not significant by Holm's correlation. ML, medial–lateral; VT, vertical; SARA, Scale for the Assessment and Rating of Ataxia; R, correlation coefficient

VT amplitude obtained by 2-time integration of acceleration showed high correlation to gait distance.

We collected representative data (e.g., mean ML amplitude during walking on a straight path, which was highly correlated with the SARA score in our previous study [13]) and subjects' clinical profiles, and their SARA and BBS scores are presented in Tables 1, 2, and 4. The total SARA and BBS scores declined at the time of observation; the SARA "gait score" changed marginally in 3 years, and the "standing score" decreased in the latter 1.5 years. The increase in total score in each patient was derived from that in the limb scores. The mean ML amplitude of gait while walking on a straight path, which we reported as the best candidate for a physiological biomarker of cerebellar ataxia, decreased with time; however, the total baseline drift in the lower back while standing with eyes open did not.

As per the above-described method, the minimal sample size estimates in each group for ANCOVA, adjusted for the baseline levels, are shown in Fig. 3. Per group, 113 patients (total sample size of 226) were required to achieve 80% power to detect a 30% reduction in ML amplitude in the first 1.5 years, while 279 patients for the total SARA score, 769 patients for the BBS score, and 1187 patients for the 6MWT gait distance were needed (Fig. 3a). However, in the final 1.5 years, as many as 1866 patients per group were required to achieve 80% power to detect a 30% reduction in ML amplitude, while 1152 patients for the total SARA score, 689 patients for the BBS score, and 2446 patients for gait distance were needed. During this period, total baseline drift measured in the lower back during standing with eyes open required the least number of patients, i.e., 58 (Fig. 3b). In the 3-year follow-up, the least number of patients was required for the SARA score (123 patients to achieve 80% power to detect a 30% reduction), while 656 patients were needed to detect a reduction in ML amplitude, 327 patients for the BBS score, 540 patients for total baseline drift in the lower back during standing with eyes open, and 1120 patients for gait distance (Fig. 3c).

ANCOVA was performed with the change in parameters obtained by the accelerometer in the 3-year follow-up as a dependent variable and sex, age at onset, disease duration, and parameters obtained by the accelerometer at baseline as dependent variables. The test results were considered significant at an α level of 0.05 for this multivariate analysis. The results of the multivariate analysis for the decline in ML amplitude were not significant, indicating that it was independent from these variables (sex, $p = 0.6976$; age at onset, $p = 0.8358$; disease duration, $p = 0.7853$; ML amplitude at baseline, $p = 0.4322$).

Discussion

In the literature, severity of gait disturbance was evaluated by Terashi et al. in Parkinson disease by acceleration, not amplitude [19]. This approach is reasonable since short steps and freezing gait are one of the major symptoms of this disorder. In cerebellar ataxia, kinesthetic feedback is disturbed. It causes abnormal joint angle control and motor exorbitance [6]. Taking this into account, we hypothesized that patients with ataxia show large ML and VT fluctuations, which correlate with the severity of cerebellar ataxia. To address this hypothesis, we assess the value of relative displacement obtained through integrating the acceleration data twice, not acceleration itself. The sensor was placed in the trunk of the patients, since degenerative ataxia generally starts with the disturbance

Table 4 Time course of SARA, BBS, and gait distance and data gained by triaxial accelerometers

	Initial evaluation	SD	1.5-year evaluation	SD	First 1.5-year interval, absolute change	ρ^{*}	3-year evaluation	SD	Second 1.5-year interval, absolute change	$\rho^{\#}$	Total 3-year absolute change	$\rho^{\$}$
Total SARA score	10.1	3.28	12.5	3.57	2.4	0.608	13.6	3.88	1.1	0.688	3.3	0.645
Berg Balance Scale score	47.4	5.20	45.9	5.53	1.5	0.790	43.5	7.67	2.4	0.777	3.9	0.571
Gait distance of 6-min walk (m)	329	108	303	116	26	0.816	292	128	11	0.948	37	0.688
Straight, mean amp. (ML) (m)	0.032	0.007	0.037	0.008	0.005	0.879	0.042	0.020	0.005	0.491	0.010	0.186
Lower back, eyes open, baseline (total) (m)	0.464	0.431	0.700	0.564	0.236	− 0.065	0.375	0.190	0.326	0.114	0.089	− 0.560

Changes in the total SARA scores, Berg Balance Scale score, gait distance, ML amplitude, and total baseline drift in the lower back while standing with eyes open. ρ^{*}, correlation of the initial and 1.5-year evaluations; $\rho^{\#}$, correlation of the 1.5-year and 3-year evaluations; $\rho^{\$}$, correlation of the initial and 3-year evaluations. Abbreviations: *amp* amplitude. Other abbreviations are the same as those in Fig. 1 and Tables 1 and 2

of gait and balance, not limb kinetic movements, and laterality of symptoms is exceptional.

The vast amount of literature on inertial sensors indicates that they analyzed acceleration directly, e.g., RMS along each of the three axes [14, 15]. Therefore, we re-evaluated the accelerometer data from our initial 25 patients with SCD by calculating RMS acceleration along each axis, but it had a weaker correlation to the SARA score compared to the mean ML amplitude of the upper back in a straight gait. Generally, patients with ataxia had a wide-based gait, resulting in large ML movements, but motion-capturing devices, such as KINNECT® (Microsoft Corporation, Redmond, WA, USA), cannot measure ML amplitude more accurately than triaxial accelerometers. Therefore, we continued to use accelerometric data integration. Clinically, several rating scales for cerebellar ataxia are used to determine the effects of therapeutic intervention trials. However, a considerable number of patients are necessary to determine its effect when using category characteristic rating scales compared with a metric variable scale [20].

We previously reported gait analysis using triaxial accelerometers as a candidate metric variable biomarker [13]. Fazio et al. reported that mean acceleration during gait measured on the sternum and in front of and behind the S2 vertebral level in patients with Parkinson's disease and those with SCD was significantly lower than that in healthy controls [21]. Matsushima et al. reported that step regularity and degree of body sway were strongly correlated with SCD duration and diagnosis of multiple system atrophy cerebellar type, respectively [22]. Hickey et al. reported the validity of accelerometers for the assessment of ataxia [23]. However, no study has investigated ataxia using accelerometers over a long period. Here, we report on the first-time changes over a time course of 3 years in patients with SCD and compared these changes with those observed using conventional rating scale scores.

As far as judging from the data from the first 1.5-year observation, it is reasonable that ML amplitude evaluation requires fewer patients than SARA evaluation, because ML amplitude is a metric variable and the SARA is a category characteristics scale. In the latter 1.5 years, sample size estimation showed that ML amplitude evaluation required a sample size similar to those in other parameters or rating scales, e.g., total baseline drift in the lower back while standing with eyes open. This drift evaluation was not considered a physiological biomarker candidate in our previous study because it did not significantly correlate with the total SARA score. In the latter 1.5 years, the estimated sample size was smaller than that needed in the first 1.5 years. This is because the absolute changes were greater in the accelerometer-acquired data, e.g., ML.

In the final 1.5 years, 11 patients who participated in our previous study dropped out because disease progression resulted in the inability to safely walk alone for 6 min, creating a bias because patients whose gait deteriorated were excluded. During this period, the data acquired by triaxial accelerometers were

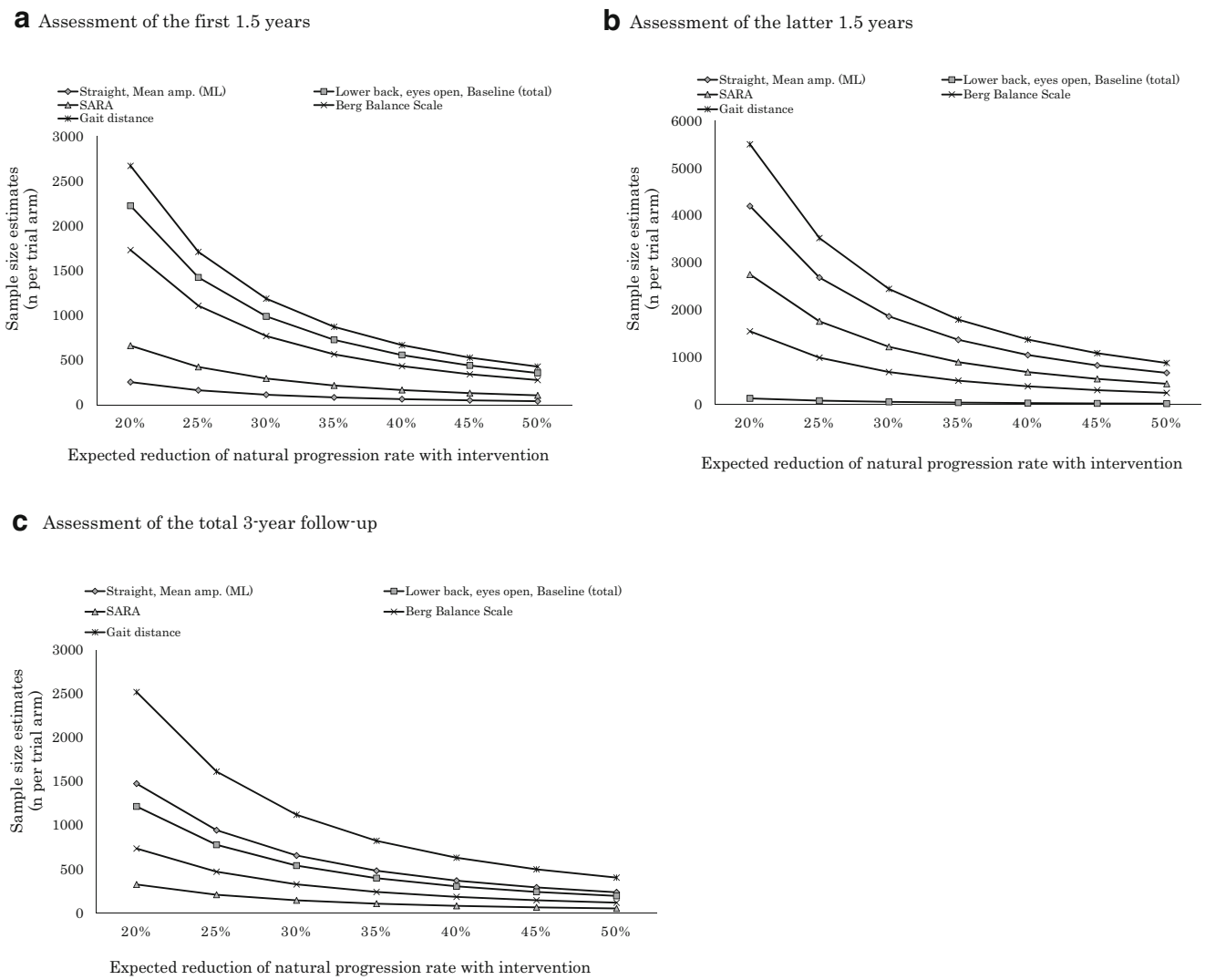

Fig. 3 Sample size detectable for the effect of clinical intervention, as estimated by ANCOVA adjusted for baseline to achieve 80% power. **a** Assessment of the first 1.5 years. Medial–lateral (ML) analysis required the least number of patients. **b** Assessment of the latter 1.5 years. Total baseline drift required the least number of patients. **c** Assessment of the total 3-year follow-up. ML analysis and standing drift required the greatest number of patients than SARA. SARA, Scale for the Assessment and Rating of Ataxia; BBS, Berg Balance Scale

more reliable when the patients stood alone with their eyes open than with their eyes closed. However, the change in these data was nonlinear; it increased in the first 1.5 years but decreased in the final 1.5 years. These data may not reflect clinical symptoms.

In the total follow-up period of 3 years, SARA analysis required fewer patients than ML amplitude analysis. We excluded patients whose symptoms worsened and could not perform the 6MWT. In addition to locomotive function, the SARA scale covers other disturbances, such as standing, upper limb function, and speech, which become apparent with disease progression and cannot be evaluated by the present gait analysis.

The mean ML amplitude was significantly correlated with the total SARA score and its gait subscore. In this patient group, the mean ML amplitude increased, whereas the gait score did not. This implies that ML amplitude is more sensitive than the SARA gait subscore in the evaluation of ataxia at an early stage. When compared to the normal control, both values obtained by integrating ML twice (CV) and RMS showed low VT value, and these two values highly correlate with the severity of gait disturbance. As an explanation of this correlation, it is likely that reduced limb muscle tone in cerebellar ataxia affects the strength of kicking the floor during walking. Another possibility is that dysmetria relates to the increase in ML amplitude itself and compensatory reduction of VT values. We previously reported that the SARA score did not correlate with the total length traveled or RMS area of body sway as measured by body stabilometers [12]. The result in our previous study coincides with that of the present study obtained by using triaxial accelerometers. In addition to the cerebellar system, gait was controlled by various neural networks, i.e., frontal and parietal cerebral cortex system, brainstem, vestibular system, and spinocerebellar pathway. It

is presumed that the cerebellum plays as a key center for organizing whole tasks, and there should be a fine functional localization on each region of the cerebellum [24].

In this study, we reported that the responsiveness of ML in patients with SCA6, SCA31, sporadic CCA, and DCCA was higher than that of SARA in 1.5 years' observation, according to the ANCOVA sample size estimation. Although cerebellar ataxia is the most dominant and common presentation in these disorders, there are still some differences in clinical presentation. For example, frequent positioning nystagmus is common in SCA6 but rare in SCA31 [25]. Therefore, further study with extensive number of subjects is mandatory. Moreover, an evaluation that there might be other biomarkers relating to various SCA genotypes or phenotypes is needed.

Generally, symptoms of degenerative ataxia begin with disturbance of gait and balance and then extend to dexterity of limb movement, speech, and others, along with disease progression. Therapeutic intervention is likely more effective at early than advanced stages. A longitudinal study in the homogeneous cohort in disability, SCA genotype and clinical phenotype, will provide more concrete evidence in regard to reliability of gait analysis. Clinical trials will be considerably facilitated by introduction of sensitive measures in assessing the effect of therapeutic intervention. In this regard, gait analysis by triaxial accelerometers will be complementary in evaluating its effects by conventional scales based on symptomatology and ADL disturbance.

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Compliance with Ethical Standards

This clinical study was approved by the ethics panels of Hokkaido University Hospital and Kushiro Rosai Hospital.

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