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Gait impairment precedes clinical symptoms in spinocerebellar ataxia type 6

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Abstract

Background—Spinocerebellar ataxia type 6 (SCA6) is an inherited ataxia with no established treatment. Gait ataxia is a prominent feature causing substantial disability. Understanding the evolution of the gait disturbance is a key step in developing treatment strategies.

Methods—We studied nine gait variables in 24 SCA6 (6 pre-symptomatic; 18 symptomatic) and 24 controls and correlated gait with clinical severity (pre-symptomatic and symptomatic).

Results—Discrete gait characteristics precede symptoms in SCA6 with significantly increased variability of step width and step time, while a more global gait deficit was evident in symptomatic individuals. Gait characteristics discriminated between pre-symptomatic and symptomatic individuals and were selectively associated with disease severity.

Conclusions—This is the largest study to include a detailed characterisation of gait in SCA6, including presymptomatic subjects, allowing changes across the disease spectrum to be compared. Selective gait disturbance is already present in SCA6 before clinical symptoms appear and gait characteristics are also sensitive to disease progression. Early gait disturbance likely reflects primary pathology distinct from secondary changes. These findings open the opportunity for early evaluation and sensitive measures of therapeutic efficacy using instrumented gait analysis which may have broader relevance for all degenerative ataxias.

Keywords

Gait; SCA6; ataxia; presymptomatic; symptomatic

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Introduction

Spinocerebellar ataxia type 6 (SCA6) is a common form of autosomal dominant ataxia presenting in adults 1, and is due to a pathological expansion of the polyglutamine-encoding CAG repeat in the *CACNA1A* gene. There are no therapeutic treatments aimed at disease modification for SCA6 at present, and clinical management remains supportive. Gait ataxia is one of the most prominent early features of SCA6, and eventually leads to loss of mobility, independence and increased falls 2, 3. Understanding and quantifying the gait disturbance is therefore key to developing new therapies, either for symptomatic management or disease modification. Here we report a comprehensive evaluation of gait in SCA6 across the disease spectrum including pre-symptomatic carriers, providing novel insight into the disorder, and a model for the evaluation of other degenerative ataxias.

Materials and Methods

Subjects and recruitment

We recruited 24 participants known to harbour a pathological expansion of the CAG repeat in *CACNA 1A.* Six were identified through predictive counselling and genetic analysis and were asymptomatic at the time of this study ($SCA6^{Pre}$), as determined by a normal neurological examination (including eye movements), no episodic complaints and an International Classification of Ataxia Rating Scale (ICARS) score < 7, reflecting values for control participants without SCA6.4 Eighteen presented to neurology services with a progressive ataxic disorder ($SCA6^{Clin}$). All mutation carriers had the same repeat length and were likely to have descended from a single common founder. 5 $SCA6^{Clin}$ were symptomatic with an ICARS score > 10 reflecting mild ataxia.4 Inclusion criteria were ability to walk 25m independently, and able to comply with testing. Exclusion criteria were presence of co-morbidities affecting mobility and poor hearing. We recruited 25 age matched healthy controls by advertisement. Institutional ethical approval and written informed consent were obtained.

Demographic and clinical measures

The following additional measures were undertaken: disease severity using the ICARS, a valid and reliable scale to assess ataxia4; height; weight; body mass index; balance confidence using the Activities Balance Confidence Scale (ABCS)6; and retrospective falls (on questioning over previous 3 month period).

Gait Evaluation

Participants performed four 12m walks at their comfortable walking pace. Practice trials were allowed to overcome anxiety or learning. Gait was measured using a 7m long instrumented mat (Platinum model *GAITR*ite, software version 4.5, CIR systems, USA), placed in the centre of 12m walkway. The *GAITR*ite system has a spatial accuracy of 1.27cm and temporal accuracy of 1 sample (240hz, ~4.17ms) and is a valid and reliable method for measuring gait. 7*Data processing and analysis*: We carried out a comprehensive analysis of gait according to a predefined model with five domains hypothesised to reflect

independent features of the neural control, providing a theoretical framework to understand pathophysiology. 8Variables included: Step velocity, step length, cadence, step time asymmetry, step length variability (SD), step time variability (SD), step width, step width variability (SD), and step length asymmetry. Variability was expressed as the within person standard deviation (SD) from left and right steps combined. The combined standard deviation of left and right steps was calculated by taking the square root of the mean variance of the left and right steps to avoid confounding step-to-step variability with variation originating from asymmetry between left and right steps. Data were extracted from *GAITR*ite using Microsoft Access 2007 as described.9 A minimum of 40 steps was included for each participant. 9 Data across trials were averaged for each variable. Non-parametric Kruskal-Wallace tests were used to test for group differences in gait characteristics. Post-hoc Mann Whitney U tests were considered significant if $p < .05$ after Holm-Bonferroni corrections. Associations between gait and disease severity were assessed using Spearman Rho correlations. To accommodate for multiple correlations, only correlations with a $p < .01$ were considered statistically significant.

Results

Demographic and clinical data are summarised in table 1. On average, the $SCA6^{Pre}$ subjects were younger than controls, and the $SCA6^{Clin}$ group were older than the controls. $SCA6^{Pre}$ subjects had a lower mean BMI than controls, but the mean BMI in $SCA6^{Clin}$ subjects was greater than controls. $SCA6^{Pre}$ and $SCA6^{Clin}$ participants had significantly reduced balance confidence compared to controls (increased ABCS). The $SCA6^{Clin}$ group were also more likely to have fallen in the previous 3 months, and one $SCA6^{Pre}$ reported a fall.

Descriptive gait data and statistical comparisons are shown in table 2 (individual data are shown in supplementary figure 1 online). When compared to controls, the $SCA6^{Pre}$ group had significantly increased variability of step time and step width, and a marginally significant increase in step length variability. All other characteristics were no different to controls. The $SCA6^{Clin}$ group were globally impaired in every gait characteristic (except for step length asymmetry) when compared to controls. Gait in $SCA6^{Clin}$ was also significantly more impaired than $SCA6^{Pre}$ except for step width variability and step length asymmetry.

After applying a more stringent p value (.01) to correct for multiple correlations, we found that a higher ICARS score ($SCA6^{Pre}$ and $SCA6^{Clin}$ combined) correlated with reduced velocity (-.522; p=.009) and step width (.735; p<.001), and a more variable step time (.580; p=.003). Scatterplots are show online in supplementary figure 2 available online.

Discussion

Here we provide the largest and most comprehensive study of gait in SCA6 to date. Our findings show increased variability in pre-symptomatic carriers for the first time reflecting early indication of primary cerebellar pathology. Given that the gait variability was more pronounced in affected individuals and correlated with established measures of severity, our findings suggest that gait measurement may provide a clinically meaningful surrogate

marker of disease that could be useful in natural history studies, and may also prove valuable in monitoring the effects of therapy, particularly in the pre-clinical stage of the disease.

The increased step time and step width variability is highly likely to be a direct consequence of cerebellar Purkinje cell dysfunction, which is known to cause subtle timing deficits.10 Step variability reflects the magnitude of step to step fluctuations, and is consistent with the role of the cerebellum in motor control.11 Increased variability of step time contributes to inconsistent stepping12, while step-width variability contributes to lateral instability, which is a marker of postural control.8, 13. Postural control has also been reported as an important feature of SCA6.14 These changes are not evident on clinical testing but are prescient of future dysfunction. Testing $SCA6^{Pre}$ under more challenging conditions therefore reveals subtle changes which are not identified with clinical scales such as the ICARS and therefore show promise as early surrogate markers of disease. Implicit changes in self-efficacy (balance confidence) may also be sensitive to these early subtle features. The findings also highlight a need for earlier intervention when there is greater opportunity to mitigate secondary consequences.

A strength of this study was the inclusion of a homogenous cohort of patients with spinocerebellar ataxia, in contrast to previous reports where ataxias of mixed etiology and disease severity have contributed to inconsistent findings. In $SCA6^{Clin}$ gait was globally impaired in agreement with others 3, 15, 16 and gait characteristics were also sensitive to disease progression, discriminating $SCA6^{Pre}$ and $SCA6^{Clin}$, a feature not previously reported. Global changes in $SCA6^{Clin}$ most probably reflect a mix of primary deficits arising from cerebellar pathology and secondary changes due to deconditioning, which are potentially amenable to therapy.17

Step velocity, step width and step time variability were significantly associated with the total ICARS score showing sensitivity to disease progression. This suggests they may be valid surrogate markers of disease severity and clinical efficacy. In support of this a case series in two patients with *CACA 1A* mutations showed that stride time variability improved with administration of 4-aminopyridine (a reversible potassium channel blocker).3 Step width variability was an early feature that did not change with disease progression (no difference between $SCA6^{Pre}$ and $SCA6^{Clin}$) and consequently was not related to the ICARS. Very early change may therefore be undetectable with the ICARS however this feature warrants further investigation as an early marker of disease.

We had a small sample size due to the rare condition, which was especially so for the pre-symptomatic group (n=6). Our findings should therefore be considered with this in mind. We adopted a conservative approach to data analysis using non-parametric statistics and adjusting for multiple comparisons allowing us to be confident in our findings. Age and BMI may be potential confounders, however, this is unlikely because the $SCA6^{Pre}$ group were younger and lighter than controls and more importantly, strongly suggests the findings relate to the underlying pathology. There was a little overlap in age between pre-symptomatic and symptomatic subjects. On interview and clinical testing the pre-symptomatic subjects were not experiencing any symptoms. One person in the $SCA6^{Pre}$ group reported a single fall however we did not collect detailed falls data and therefore are unable to ascertain the cause

of the fall. We evaluated participants at preferred walking speed where the effects of gait speed on variability are reduced to avoid the confounding influence of high and low velocity on gait variability in ataxia. 3, 18Furthermore SCA6^{Pre} and controls walked at similar speeds making this an unlikely confounder. Finally, this was a cross sectional study. Longitudinal studies are needed to quantify the natural progression of gait disorder in SCA6 as well as validate gait as a sensitive marker of disease progression and its responsiveness to intervention.

In summary, this is the largest study to include a detailed characterisation of gait in SCA6, including presymptomatic subjects, allowing changes across the spectrum to be compared. Selective gait disturbance is already present in SCA6 before clinical symptoms appear and gait characteristics are also sensitive to disease progression. Discrete features of gait may therefore have a role as markers of disease and disease progression with potential across a broader spectrum of ataxias warranting further investigation. Our findings also suggest therapy should start at an earlier stage when there is greater potential to rectify, as much as possible, primary pathology and to enhance compensatory patterns, and gait analysis will provide a sensitive surrogate marker for clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Summary of participant characteristics (Mean ± SD) or Median (Quartiles).

Variable	Controls (n = 25)	SCA6	
		SCA6^{Pre} n = 6	SCA6^{Clin} n = 18
Age (years)	50.2 ± 12.2	42.33 ± 14.6	61.5 ± 8.5 * ǂ
Sex	f 17, m 8	f 4, m 2	f 13, m 5
Falls history	(0/25)	(1/6)	(4/18)
Height (m)	1.67 ± .09	1.67 ± .09	1.65 ± .08
Body mass (kg)	74.1 ± 13.7	71.6 ± 15.5	78.8 ± 12.5
Body mass index	26.6 ± 4.6	24.6 ± 2.9	28.6 ± 3.7 †
Disease Duration	-	-	3.7 ± 3.2
ABCS (0-100)	96.0 ± 3.7	86.3 ± 8.1 *	59.2 ± 24.3 *†
ICARS (0-100)			
Total		3 (1, 3)	20.5 (13.75, 20.5) †
Gait and Posture		1 (.75, 1)	7.5 (6, 7.5) †
Kinetic		0 (0, 0)	6 (4, 6) †
Speech and Language		0 (0, 0)	1 (0, 1) †
Oculomotor		0.5 (0, 0.5)	2.5 (2, 2.5) †

* = significant difference from controls ($p < .05$)

ǂ = significant difference from SCA6^{Pre} ($p < .05$)

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Table 2

Descriptive data and statistics for between group comparisons for all gait variables (median (quartiles)).

Gait Domain	Variables	Controls	SCA6^{Pre}	SCA6^{Clin}	Kruskal-Wallis test (*p*)	Control v SCA6^{Pre} (*p*)	Control v SCA6^{Clin} (*p*)	SCA6^{Pre} v SCA6^{Clin} (*p*)
Pace	Step velocity (m.s^{-1})	1.47 (1.34, 1.64)	1.50 (1.27, 1.59)	.95 (.80, 1.19) *†	< ***.001***	.751	< ***.001***	***.002***
	Step length (m)	.76 (.69, .80)	.75 (.65, .80)	.55 (.42, .66) *†	< ***.001***	.510	< ***.001***	***.015***
Rhythm	Cadence (steps.min^{-1})	119 (112, 128)	117 (112, 123)	103 (98, 109) *†	< ***.001***	.827	< ***.001***	***.002***
Asymmetry	Step time asymmetry (ms)	5.75 (1.97, 1.31)	3.82 (1.47, 11.26)	12.66 (8.94, 16.64) *†	**.010**	.751	***.007***	***.015***
Variability	Step length variability (m)	.013 (.011, .017)	.020 (.014, .025) *	.032 (.024, .041) *†	< ***.001***	*.053*	< ***.001***	***.001***
	Step time variability (ms)	10.26 (8.35, 12.31)	12.67 (11.14, 16.18) *	24.43 (19.02, 38.44) *†	< ***.001***	***.023***	< ***.001***	***.015***
Postural	Step width (m)	.085 (.063, .100)	.087 (.052, .101)	.136 (.100, .193) *†	< ***.001***	.827	< ***.001***	***.002***
	Step width variability (m)	.016 (.014, .019)	.024 (.020, .025) *	.022 (.019, .032) *	< ***.001***	***.004***	< ***.001***	.974
	Step length asymmetry (m)	.012 (.004, .021)	.017 (.004, .033)	.022 (.007, .045)	.145	.419	.061	.415

Raw *p* values are presented. Significant group differences after Holm-Bonferroni corrections are highlighted in bold italics;

* = significant difference from controls;

† = a significant difference from SCA6^{Pre}.