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Stance instability in preclinical SCA1 mutation carriers: A 4-year prospective posturography study

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ABSTRACT

Objective: We aimed to study postural balance in preclinical Spinocerebellar ataxia type 1 (SCA1) mutation carriers to identify and observe specific motor functional deficit before evident clinical manifestation.
Methods: Participants were 9 asymptomatic SCA1 mutation carriers (6 M/3F), aged 31.8 ± 7 years (range 22–44), and 17 age-matched non-carrier controls (5 M/12F) (age 18–42). Subjects underwent postural tests on a force platform (Tetrax®-IBS, Sunlight Medical Ltd.) with and without visual feedback. Amount of body sway was represented by stability index (ST). Tests were repeated after 2- and 4-years. Estimated years to onset were calculated.
Results: In controls, ST was unchanged from baseline to 4-year evaluations in all standing conditions. SCA1 mutation carriers performed similarly to controls in the postural tasks with open eyes, whereas in conditions without visual feedback SCA1 carriers had significantly higher ST than controls at all longitudinal evaluations. Close-to-disease onset carriers (≤7years) showed more prominent time-dependent stance abnormalities ($p < 0.0001$ for all comparisons).
Conclusions: Traceable and progressive postural abnormalities can be observed in preclinical close-to-onset SCA1 carriers. Quantitative analysis of stance could represent a promising outcome measure in clinical trials including preclinical subjects.

1. Introduction

Spinocerebellar ataxias (SCAs) are heterogeneous adult-onset hereditary neurodegenerative diseases. The individuals who inherited the mutation from their parents usually experience a period of several decades free of neurological deficits before manifesting the characteristic symptoms of the diseases [1,2]. The identification of the causing mutations has improved diagnostic procedures and allowed the recognition of the mutation carriers before clinical symptoms are noticed (preclinical phase) [1]. Postural instability is the most frequent initial clinical manifestation of cerebellar ataxia promptly recognized by the patients as a marker of disease onset [1,2]. Quantitative posturography has been performed in SCA affected patients, using different balance equipments, whereas in SCA preclinical mutation carriers only a limited number of posturographic investigations have been reported [2,3].

The aim of this study was to test efficacy and usefulness of posturography as outcome measure in future pharmacological trials considering the preclinical phase of SCA diseases.

2. Subjects and methods

2.1. Subjects

We recruited 26 family members of genetically diagnosed SCA1 patients. To be eligible for the study, individuals had to be directly related to individuals with SCA1, have no ataxia (score on the Scale for Assessment and Rating of Ataxia, SARA < 3) [4], and age > 18 years. All participants knew to have 50% risk of carrying the SCA1 mutation, but they had the choice to know about their genetic status or not. Participants who decided to know the result of the genetic test were offered genetic counseling and psychological support, in agreement with the recommendations for predictive genetic test [5,6]. Only two

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subjects decided to know their genetic status. Genetic results of the other participants were not disclosed to the personnel who performed clinical and posturography evaluations. SARA scale was administered by neurologist expert in ataxia. Clinical and posturography evaluations were performed at baseline, and at 2-year and 4-year intervals (± 3 months).

Nine participants (6 M/3F, age 32 ± 7 years) carried the SCA1 mutation (41–51 CAG repeats), and 17 were non-carrier controls (5 M/12F; age 28 ± 9 years).

Estimated years to-disease-onset were calculated according to the described model [7]. The study was approved by the local ethic committee and written informed consent was obtained from participants. Consent form included clear information regarding hereditary transmission, percentage of genetic risk and clinical characteristics of SCA1 disease. All participants had the opportunity to extensively discuss with the neurologist and geneticist about their genetic risk and the purposes of the study.

2.2. Posturography assessment

Posturography was recorded using the Tetrax® Interactive Static Posturography System (Sunlight Medical Ltd., Tel Aviv, Israel), consisting of four sensor platforms that record right and left heel and toe applied forces to the ground. Subjects were requested to stand on a solid surface and on a foam pad with and without visual feedback. System computes a general stability index (ST), representing the quotient of the sum of the amplitudinal changes (body sway), in microvolts, divided by body weight. A lower ST indicates smaller fluctuations and therefore better postural control [8–10].

2.3. Statistical analysis

Statistical analyses were performed with JMP® 11.2.0 (SAS Institute Inc., United States). Wilcoxon-Kruskal-Wallis tests were used for comparing demographic data. Multivariate Analysis of Variance for repeated measures (MANOVA) was performed for the comparison “within groups” and “between groups”, followed by the Tukey-Kramer HSD (Honest Significance Difference) post-hoc analysis. Correlations between posturography and clinical variables were analyzed using Spearman's rho test. P-values ≤ 0.05 were considered significant.

3. Results

3.1. Clinical evaluation

All enrolled subjects (17 controls, 9 SCA1 carriers) completed the 2- and 4-year follow-up examinations (2yFU, 4yFU). At baseline none of the SCA1 carriers had neurological symptoms, 7/9 had mildly increased deep tendon reflexes, 1/9 had horizontal gaze nystagmus. The estimated years-to-disease onset ranged from −3 to −16 years (median −7). After 2 years, 1/9 SCA1 carrier manifested mild signs of ataxia with SARA score = 3, and at 4yFU two additional subjects had SARA score = 3.

3.2. Posturography

The posturographic measures are summarized in Table 1 and Fig. 1.

In controls, ST did not differ from baseline to 4yFU evaluations in any of the four standing conditions (Fig. 1, graphs A–D). In the postural tasks with open eyes, the SCA1 carriers had ST similar to controls, from baseline to 4yFU (Fig. 1, graphs A, C).

In the standing conditions with closed eyes, SCA1 carriers had higher ST mean values than controls at all evaluations but a statistically significant difference was found only at 4yFU (p = 0.014 solid surface, p = 0.01 foam pad) (Fig. 1, graphs B, D). The comparison for longitudinal repeated measures within the SCA1 group showed a significant increase of ST from baseline to 4yFU in the conditions with closed eyes, both on solid surface (p = 0.046), and on foam pad (p = 0.01).

ST indexes were neither correlated with age at examination nor with estimated years to-disease-onset in the SCA1 group. When we analyzed separately the mutation carriers “far-from-onset” (> 7 years from estimated onset) and “close-to onset” (≤7 years from estimated onset), we could demonstrate that far-from-onset SCA1 carriers had ST indexes comparable to controls, whereas close-to-onset carriers had always significantly higher ST than other groups in stance conditions with closed eyes, (p < 0.0001, for all comparisons), with a time-dependent worsening from baseline to 4yFU (Fig. 1, graphs F, H) (p < 0.005 on solid surface; p < 0.015 and on foam pad). On solid surface with open eyes, the close-to-onset carriers differed from the other subjects only on foam pad at 4yFU (p < 0.022) (Fig. 1, graphs E, G).

Table 1
Longitudinal postural parameters and SARA scores in SCA1 mutation carriers and controls.

Stance Conditions	Subject groups	Posturography Stability Index		
		Baseline	2 year follow-up	4 year follow-up
Solid Surface	**Controls** (n.	16.20 (6.9)	16.20 (7.4)	16.00 (6.0)
Open	17)	16.10 (6.6)	18.84 (8.1)	20.05
Eyes	**SCA1 carriers**	22.68(2.8)	24.69 (3.1)	(10.5)
	(n. 9)	10.83 (1.8)	14.17 (7.9)	29.92 (7.4)
	Close-to-onset			12.15 (2.1)
	(n.4/9)			
	Far-from-onset			
	(n.5/9)			
Solid Surface	**Controls**	19.25 (7.7)	21.66 (8.0)	21.48 (7.5)
Closed Eyes	**SCA1 carriers**	25.31 (15.3)	33.40	38.60
	Close-to-onset	40.74 (6.4)	(16.2)	(22.6)
	Far-from-onset	12.97 (2.6)	47.36	61.86 (3.8)
			(8.60)	19.99 (5.9)
			22.23	
			(10.8)	
Foam Pad	**Controls**	18.61 (4.1)	17.78 (6.2)	8.82 (9.2)
Open	**SCA1 carriers**	21.51 (9.4)	19.94 (7.0)	22.21
Eyes	Close-to-onset	30.61 (2.7)	25.49 (5.4)	(11.8)
	Far-from-onset	14.24 (4.5)	15.51 (4.6)	31.5 (12.0)
				14.71 (3.3)
Foam Pad	**Controls**	26.93 (6.7)	22.97 (6.2)	25.72 (9.1)
Closed Eyes	**SCA1 carriers**	37.50 (17.9)	41.82	49.34
	Close-to-onset	55.68 (3.1)	(27.8)	(27.8)
	Far-from-onset	22.96 (6.0)	66.96	78.10 (4.2)
			(22.5)	26.33 (6.3)
			21.72 (4.7)	
SARA Scale				
N. Subjects presenting score ≥3				
Controls		0/17	0/17	0/17
SCA1 carriers		0/9	1/9	3/9
Close-to-onset		0/4	1/4	3/4
carriers		0/5	0/5	0/5
Far-from-onset				
carriers				

SCA1 Far-from-onset subjects: > 7 years from estimated onset; SCA1 Close-to-onset subjects: ≤7 years from estimated onset. Mean values and standard deviation in parenthesis. SARA = Scale for Assessment and Rating of Ataxia.

4. Discussion

In spinocerebellar ataxia patients posture and gait deterioration have been extensively investigated during the course of the diseases with appropriated clinical and functional scales, however only limited quantitative posturography data are available for preclinical SCA subjects [1–3]. We used a quantitative posturography method with the aim of measuring, in SCA1 preclinical carriers, early stance abnormalities, that could be monitored as surrogate marker of disase