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ATAXIA GLOBAL CONFERENCE 2022

with focus on trial-readiness for ataxias

SUBTLE ABNORMALITIES OF GAIT AND POSTURE IN THE PRODROMAL STAGE OF SPINOCEREBELLAR ATAXIA TYPE 2

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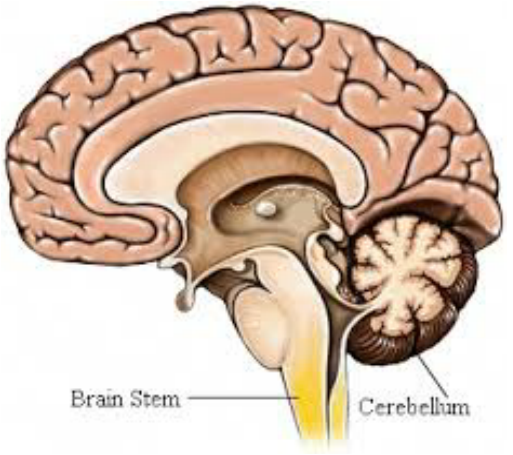
Introduction



Spinocerebellar Ataxia type 2 (SCA2)

- Produced by the increase in the number of repetitions of the CAG trinucleotide in the coding region of the ATXN2 gene, located on the long arm of chromosome 12, above 32 repetitions.

- Cerebellar dysarthria
- Dysmetria
- Adiadochokinesia
- Painful muscle contractures
- Slowing of saccadic eye movements

- **Gait and posture disorders**

Introduction

Scale for the Assessment and Rating of Ataxia
(SARA)

- Internationally widely accepted clinical method
- Allows evaluation of the severity of the cerebellar syndrome and its progression
- Allows evaluating the effect of clinical trials and therapeutic strategies

- It depends a lot on the observation and assessment of the doctor or the researcher
- Very subjective and vulnerable to error
- low sensitivity

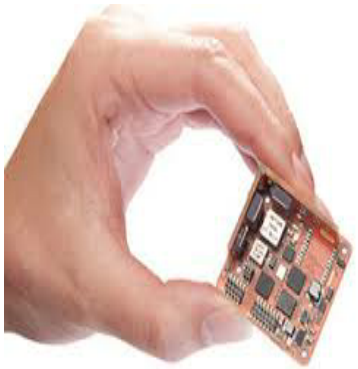
Introduction

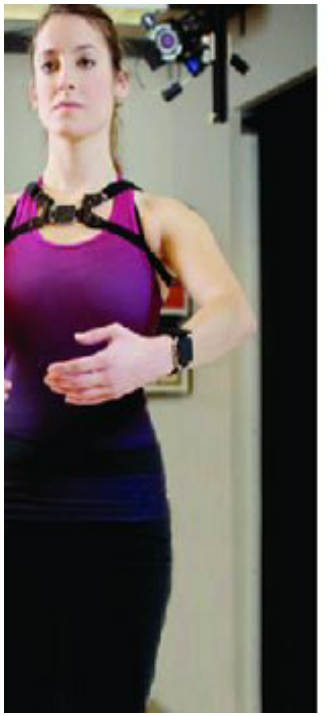
Scale for the Assessment and Rating of Ataxia
(SARA)

It is inefficient for studying and characterizing early changes in gait and posture in the prodromal stage of the disease, and therefore for the search for preclinical and progression biomarkers

Introduction

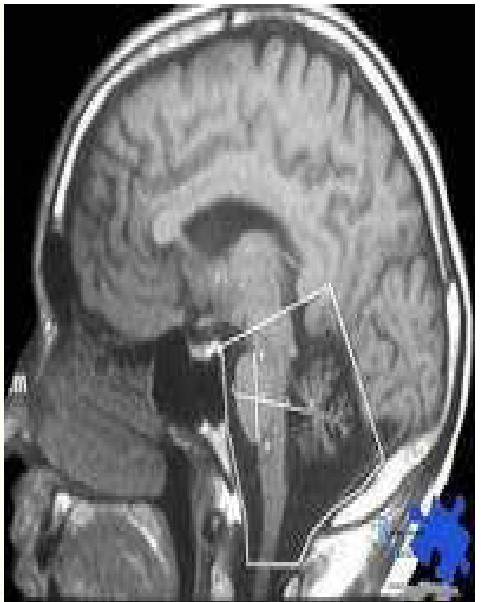
Wearable body sensor systems are increasingly being introduced into clinical practice for motion analysis due to their discreet, lightweight, eco-friendly, low-cost, and easy-to-use characteristics, as well as their ability to provide objective measurements of gait and posture

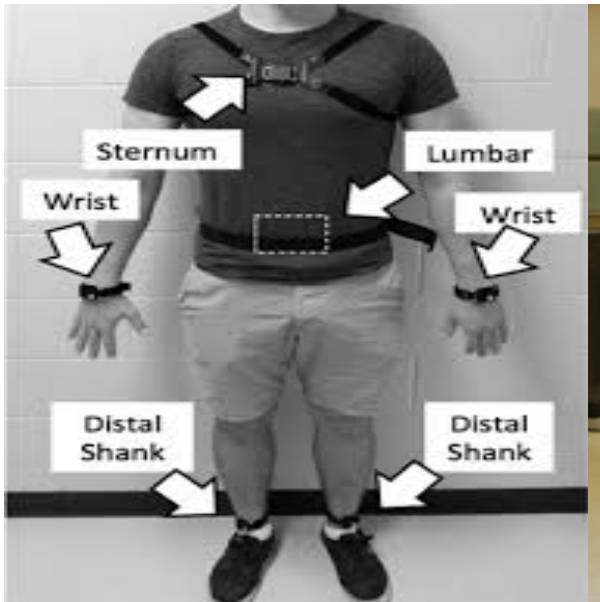




AIM

To describe new preclinical biomarkers of early gait and posture abnormalities in presymptomatic stage of SCA2





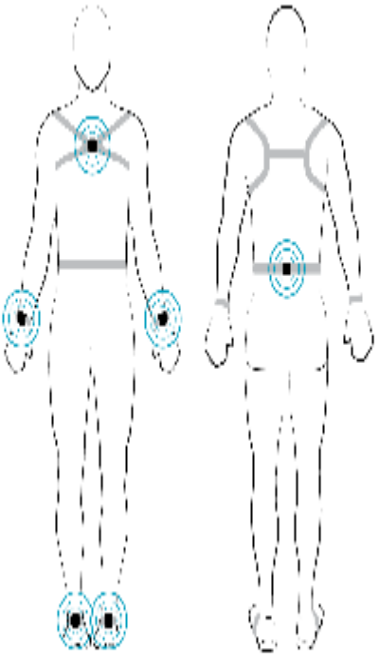
Patients and Methods

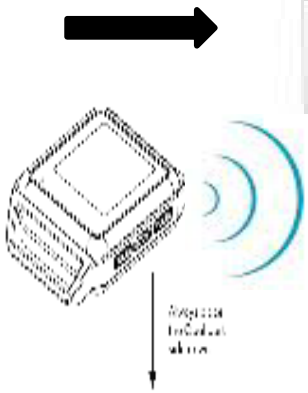
Table 1: Characteristics of the individuals who participated in the study

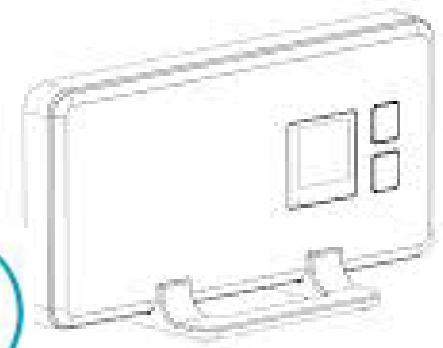
VARIABLES	Preclinical subjects	Healthy controls
N	30	30
Age (Years)	43.30 ± 10.5 (22-73)	47.30 ± 12.01 (21-74)
Estimated time to onset of ataxia (Years)	10 ± 9 (9-33)	-
Mutation size (Number of CAG repeats)	36.44 ± 1.9 (32-41)	-
SARA score (Points)	1 ± 1 (0-2.5)	0

Patients and Methods

APDM Mobility Lab







Sensors

Modulator

Software

Patients and Methods

Gait variables

- **Lower limbs:** gait speed, stride length, foot elevation at mid-swing, toe-out angle, toe-off angle, double support period, and swing period
- **Lumbar/trunk metrics**: ranges of motion in the coronal, sagittal, and transverse planes at the lumbar and trunk regions
- **Upper limbs** ranges of motion

Posture variables

- Jerks
- Mean Velocity
- Path length

Results and Discussion

Gait Analysis

Table 2: Comparison of lower limbs gait variables. Normal gait

Variables		Preclinical subjects	Healthy controls	t	p
Gait speed (m/s)	mean	1.05 ± 0.1	1.03 ± 0.1	0.47	0.637
	std	**0.06 ± 0.03**	**0.04 ± 0.01**	**2.55**	**0.016**
Stride length (m)	mean	1.09 ± 0.1	1.10 ± 0.1	-0.35	0.727
	std	**0.04 ± 0.02**	**0.03 ± 0.01**	**2.76**	**0.010**
Elevation at mid-swing (cm)	mean	**0.80 ± 0.36**	**0.60 ± 0.25**	**2.39**	**0.023**
	std	**0.33 ± 0.15**	**0.25 ± 0.06**	**2.37**	**0.024**
toe-out angle (degrees)	mean	13.47 ± 5.47	10.80 ± 8.70	1.41	0.163
	std	**3.47 ± 0.83**	**2.67 ± 0.50**	**4.50**	**0.00003**
toe-off angle (degrees)	mean	**34.32 ± 3.91**	**36.53 ± 3.52**	**-2.30**	**0.023**
	std	**1.71 ± 0.50**	**1.32 ± 0.31**	**3.67**	**0.0005**
Double support (%GCT)	mean	**21.33 ± 2.96**	**19.67 ± 2.42**	**2.27**	**0.030**
	std	**1.33 ± 0.47**	**1.06 ± 0.39**	**2.20**	**0.036**
Swing period (%GCT)	mean	**39.33 ± 1.47**	**40.16 ± 1.20**	**-2.31**	**0.028**
	std	**0.87± 0.24**	**0.66 ± 0.18**	**3.42**	**0.001**

GCT: Gait Cycle Time

Results and Discussion

Table 3: Comparison of trunk and lumbar regions gait variables. Normal gait

Variables			Preclinical subjects	Healthy controls	t	p
Coronal Range of Motion (degrees)	lumbar	mean	12.12 ± 3.33	9.22 ±2.86	3.62	0.001
		std	0.85 ±0.27	0.67 ±0.17	3.12	0.003
	trunk	mean	6.00 ±2.06	6.05 ±2.22	-0.08	0.939
		std	1.13 ±0.36	0.95 ±0.27	2.19	0.033
Sagittal Range of Motion (degrees)	lumbar	mean	6.27 ±1.94	5.81 ±2.63	0.76	0.447
		std	0.90 ±0.35	0.72 ±0.16	2.52	0.015
	trunk	mean	5.10 ±0.86	4.41 ±0.94	2.97	0.004
		std	1.19 ±0.50	1.02 ±0.38	1.51	0.137
Transverse Range of Motion (degrees)	lumbar	mean	13.29 ±4.26	10.04 ±4.78	2.79	0.007
		std	1.93 ±0.61	1.71 ±0.40	1.64	0.107
	trunk	mean	9.18 ±3.27	8.49 ±2.68	0.90	0.373
		std	1.64 ±0.53	1.58 ±0.52	0.43	0.672

Results and Discussion

No significant differences in the range of motion of the upper limbs between presymptomatic subjects and healthy controls

Results and Discussion

Tandem gait

- Significant increase in range of motion in the coronal plane in the lumbar area in presymptomatic subjects
- Significant increase in range of motion in the sagittal plane in the trunk area in presymptomatic subjects
- Significant increase in range of motion in the upper limbs in presymptomatic patients
- Significant increase in the range of motion in the transverse plane in the trunk area in the presymptomatic subjects who had a SARA score greater than 0 compared to those who obtained a SARA score of 0

Results and Discussion

Posture Analysis

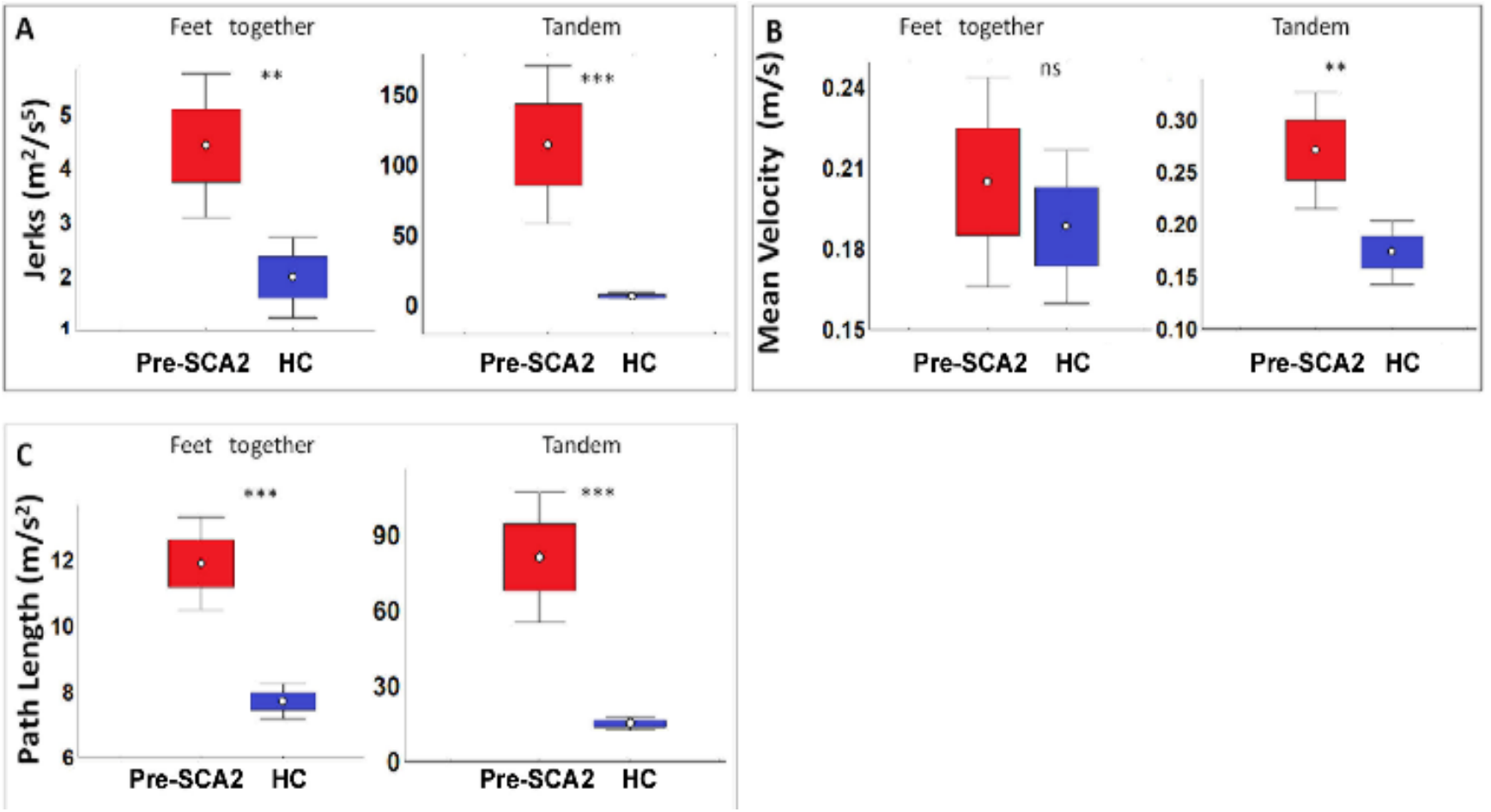


Figure 1: Posture changes in presymptomatic subjects in the feet together and tandem postures

Results and Discussion

Table 4: Correlations between normal gait variables with CAG repetitions and estimated time to onset of ataxia

Variable	Estimated time to onset	
	r	p
Toe off angle (degrees)	0,56	0,002
Gait speed variability (m/s)	-0,40	0,033
Toe out angle variability(degrees)	-0, 41	0,032
Variable	CAG repeats	
	r	p
Gait speed (m/s)	-0,48	0,018
Toe off angle (degrees)	-0,40	0,033

Results and Discussion

Most significant findings

- Increased variability in swing period, toe-off angle, and toe-out angle, reflecting significant variability between gait cycles, as a result of low rhythmicity of movement.
- Increased mean coronal and transverse ranges of motion in the lumbar position, as well as sagittal range of motion in the trunk position, resulting from hypermetric movements of axial body segments.
- Changes in gait speed, double support and swing times, reflecting compensatory mechanisms of hypermetry of the axial portion of the body.
- Early postural instability in feet together and tandem postures, reflecting early cerebellar involvement, but could also suggest involvement of somatosensory pathways and vestibular dysfunction.

Results and Discussion

Most significant findings

- Correlation analyzes revealed that decreased toe-off angle constitutes a compensatory mechanism that prevents early dynamic balance impairments revealed by increased truncal/lumbar range of motion during gait.
- There are alterations in gait and posture metrics in prodromal subjects with a zero score on the SARA scale

Conclusions

- The limited utility of the SARA score for screening for preclinical biomarkers of subtle cerebellar abnormalities was confirmed, laying the groundwork for instrumental assessment of gait and posture in presymptomatic carriers of SCA2.

- The study of gait and posture using inertial sensor systems provide quantitative parameters that help to reliably differentiate normal from pathological gait patterns and thus improve the diagnosis and monitoring of gait and posture abnormalities

- Early disturbances of gait and postural control exist in the presymptomatic stage, offering insight into this early stage of the disease and providing potential new biomarkers with substantial utility expected in future clinical trials.

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