

A longitudinal quantitative analysis of gait in patients with SCA-12

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ABSTRACT

Introduction: Spinocerebellar ataxia type 12 (SCA 12) is characterized by late onset tremor, ataxia and pyramidal signs. Parkinsonism and cognitive decline may appear with time. It is considered as slowly progressive but temporal evolution of symptoms has not been reported.

Method: We report the evolution of symptoms in three SCA12 patients followed over a range of 5–6 years. We focused on the evolution of gait abnormality as it becomes the most disabling symptom as disease advances. Two-dimensional gait parameters were studied using an electronic walkway at various time points to measure objective changes in gait.

Result: All patients presented with tremor in the upper extremity at baseline which progressed non-uniformly over the years. Progression of gait variability measures of step length, stance time and step time were also observed.

Conclusion: Gait characteristics such as variability may precede clinical gait abnormality and could serve as a sensitive marker for disease progression for better therapeutic intervention in disease management. Future studies with larger sample size should be undertaken to conclusively validate this observation.

1. Introduction

Spinocerebellar ataxia type 12 (SCA12) is a rare neurodegenerative disease caused by abnormal expansion of the CAG repeat length of the PPP2R2B gene [1]. It is a form of autosomal dominant cerebellar ataxia predominantly reported in ethnic Agarwal community originating from North India [2]. Patients with SCA12 typically demonstrate midlife onset of symptoms such as upper limb action tremor, a unique representation compared to other SCA's [3]. With disease progression, patients develop other features like head tremor, dysarthria and gait ataxia. Cognitive impairment and Parkinsonism are also reported as the disease progresses [4,5]. However, gait disturbance is one of the important causes of disability with disease advancement. A recent meta-analysis on gait characteristics in cerebellar ataxia (SCA 1,2,6,14) demonstrated that during preferred pace walking, these patients walk with reduced speed, increased base width, and increased inter-step variability as compared to healthy [6]. Gait variability is a quantitative measure of inter-step variation of gait parameters. The progression of gait abnormalities in SCA12 is not yet studied.

As compared to other SCAs, SCA12 is considered to progress slowly. A follow-up study in SCA3 reported an average of 56% increase in the

ICARS (International Cooperative Ataxia Rating Scale) score over five years [7] but similar studies have not been conducted for SCA12. We aimed to study the evolution of symptoms in three patients of SCA12 by analyzing clinical features and objective gait assessment, over a period of 5–6 years.

2. Method

The study was approved by the Institutional Ethics Committee and written informed consent was obtained from all participants according to the Declaration of Helsinki. Quantitative gait assessment was performed through an electronic walkway (GAITRite®, CIR Systems Inc., USA). Patients were asked to walk on the 500-cm-long instrumental mat at their comfortable walking pace for at least six times (3 times in each direction of mat). First two walks were excluded as they were meant to make the patient accustomed to the task. Therefore, the average of remaining 4 walks were used for further gait data analysis. The average step count was 33 for the three SCA12 patients. Gait parameters were selected based on a predefined model developed by Lord et al., 2013 [8]. The gait features were compared with an age-matched healthy cohort (n = 25) without any apparent neurological diseases or locomotive

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impairment. Mean age of the healthy group was 58.4 ± 4.0 with 13 (52%) males and 12 (48%) females. The gait variables were standardized with z-score (distance from the mean of healthy gait parameters, when measured in standard deviation units). Cognition was assessed using the MMSE (Mini Mental State Examination) scale, whereas the ICARS was used to measure the severity of disease. All three patients were examined at baseline and follow-up.

3. Patient-1

A 57-year-old man with a disease duration of 7 years had a CAG repeat length of 54. At baseline (1 year after disease onset) he presented with visible intention and postural tremor of both upper extremities and dysarthria. He had no signs of Parkinsonism. MMSE score was 27/30 while the ICARS score was 25/100. Clinically, his gait was normal with no sign of ataxia. He could perform tandem walk without any significant difficulty.

Some changes in gait parameters were noted on objective gait study. Most remarkable gait impairment at baseline was increased variability of step time and stance time. Mild increase in step width and step length were also seen. The gait speed was normal compared to healthy participants.

Upon follow-up after 6 years, both intention and postural tremor of right upper extremity had increased as compared to baseline but on the left side, no changes were observed (Table 1). No change in dysarthria was noticed. It is interesting to note a lateralized progression of disease, unlike many neurodegenerative disorders. Increase in ICARS score (28% from baseline) and 11% reduction in MMSE score were seen. His gait remained unchanged on clinical examination.

On objective gait assessment, an increase in variability of step length was most prominent at follow-up. We also observed a decrease in step length, velocity, swing time and an increase in step width and stance time (Fig. 1A).

Table 1
Changes in clinical features of three SCA-12 patients over a period of 5–6 years.

Scores and sub-scores	Baseline		Follow up	
	Patient 01			
ICARS (0–100)	25		32	
Gait (0–12)	0		1	
Dysarthria (0–8)	2		2	
MMSE (0–30)	27		24	
	Right	Left	Right	Left
Postural tremor (0–4)	1	2	3	2
Intention tremor (0–4)	2	2	3	2
	Patient 02			
ICARS (0–100)	36		40	
Gait (0–12)	1		4	
Dysarthria (0–8)	2		2	
MMSE (0–30)	24		22	
	Right	Left	Right	Left
Postural tremor (0–4)	1	2	2	2
Intention tremor (0–4)	2	3	3	3
	Patient 03			
ICARS (0–100)	37		50	
Gait (0–12)	1		9	
Dysarthria (0–8)	2		2	
MMSE (0–30)	30		27	
	Right	Left	Right	Left
Postural tremor (0–4)	0	1	1	1
Intention tremor (0–4)	1	2	2	2

4. Patient-2

A 56-year-old male with a 10-year history of onset of symptoms had a CAG repeat length of 53. On examination at baseline (after 4 years of disease onset) he had noticeable postural and intention tremor of the upper extremities. Dysarthria was also present. No Parkinsonian features were observed. MMSE and ICARS scores were 24/30 and 36/100 respectively at presentation. Clinically, his gait was normal except for mild swaying but he could perform tandem walking.

Gait analysis at baseline showed decreased step length and velocity compared to healthy individuals. Increased step width was also observed along with step time variability (Fig. 1B)

Follow-up after 5 years revealed no change in dysarthria. Increase in tremor was seen more in the right upper limb than the left, further suggestive of lateralized progression of the disease. Relatively less change in ICARS score (11%) was observed (Table1). A decrease in MMSE score (8%) was also observed. Clinically, gait was slightly more impaired with increased swaying as compared to baseline.

Upon gait analysis, the stance time variability and step length variability were remarkably increased. Surprisingly, the average step width was close to normal at follow-up.

5. Patient-3

A 65-year-old male with a disease duration of 13 years had a CAG repeat length of 62. At baseline examination (6 years after disease onset), he had intention and postural tremor along with dysarthria. His baseline MMSE score was 30/30 and his ICARS score was 37/100. On clinical examination, gait was impaired with unequal sideways steps along with difficulties in half-turn and tandem walking. Grade 2 bradykinesia was observed for both hands

Gait analysis revealed increased step time and stance time variability. Reduced velocity and step length were reported as compared to matched healthy at baseline. Notably, the step width was not altered in this patient (Fig. 1C).

At follow-up (after 6 years), dysarthria remained unchanged. The severity of intention and postural tremor increased on the right side but remained the same for the left side. Increase in ICARS score (35%) was observed showing the slow disease progression trend similar to other cases. A decline in cognitive function (10%) was also seen through the MMSE score (Table 1). Clinical examination revealed further worsening of gait as compared to baseline.

After 6 years, increase in stance time and step length variability were noticed. The velocity and step length were reduced. Left-right asymmetry was observed in gait parameters in the follow-up visit, suggestive of a lateralized progress of the disease.

6. Discussion

Through this case series, we provide a longitudinal study of gait and other non-ataxic symptoms in SCA12. The slow progressive nature of this type can be observed through relatively mild worsening of the disease in all three patients.

These cases reveal that objective gait assessment could be a sensitive tool for disease progression. Our result is in accordance with previous studies in SCA 6 (Table 2) and other ataxias where gait variability was affected before clinical gait abnormality [9]. Increased variability measures were seen in all three patients at baseline which worsened progressively over time. Step time variability contributes to erratic stepping and is grossly abnormal at baseline, hence further changes could not be appreciated on follow-up as seen in Fig. 1. Decrease in velocity and step length at follow-up was also observed. Step width was increased in patients 1 & 2, but surprisingly it decreased in patient 3. This increase in step width could be a compensation for instability as seen in ataxic gait. While in patient 3, the step width was decreased possibly because of coexisting Parkinsonism. Overall, our findings

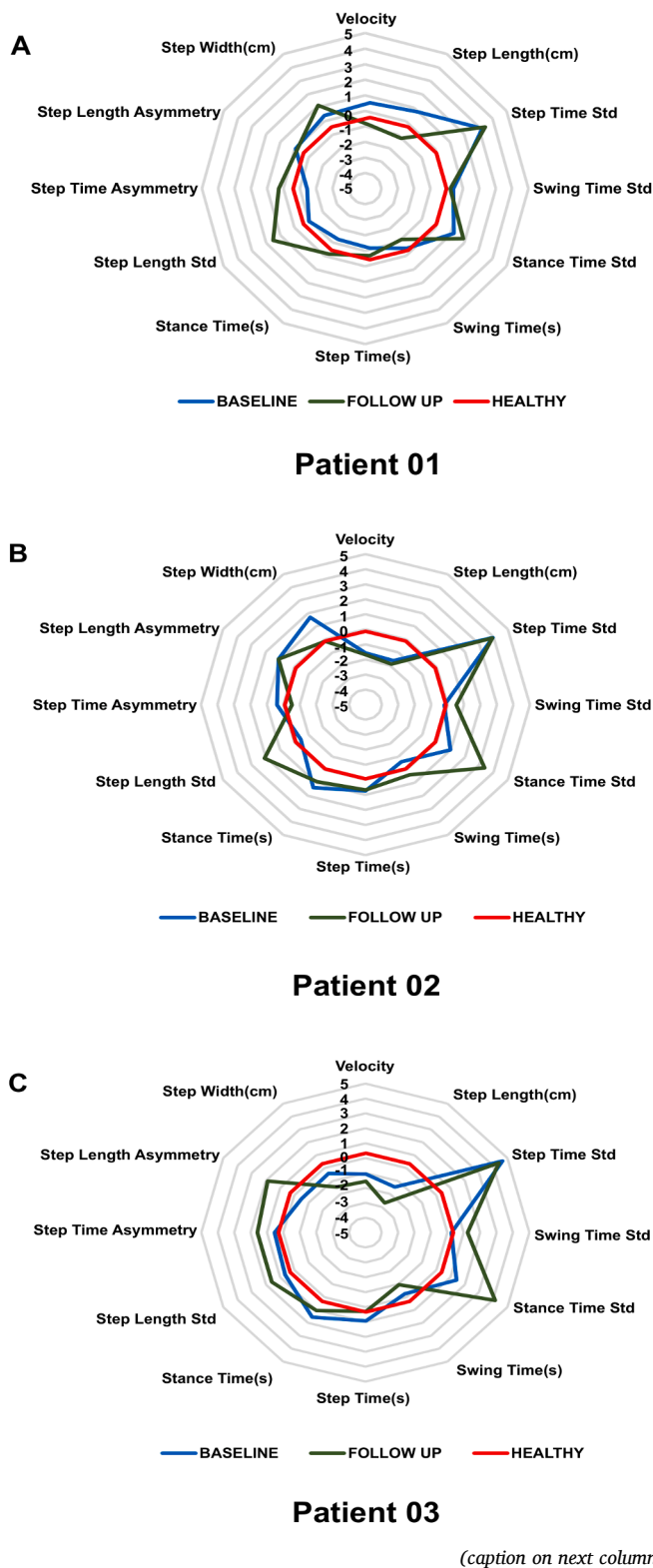


Fig. 1. Radar plot of patients with SCA12 depicting the longitudinal changes in gait parameters. The plots show the z scores of various gait parameters in reference to the age-matched neurologically healthy controls. The gait variables were standardized using z score. Std = standard deviation an index of gait variability. A. Shows the longitudinal changes of gait parameters over a follow-up period of six years. The red colour depicts the reference z score of age-matched healthy control. The blue colour represents the baseline gait parameters in patient 01. This shows that Step time Std and Stance time Std is already impaired in this patient during his baseline visit. The Step length std (shown in green) increased from the baseline at six years follow-up visit. B. Baseline visit (shown in blue) depicts impairment in Step time Std and Stance time in patient 02. Increase in Step length Std and Stance time Std are seen at follow-up (shown in green) after 5 years. C. In patient 03, impairment in Step time Std and Stance time Std are observed at baseline (shown in blue). At follow-up (shown in green) after 6 years impairment is seen in Step length Std and Stance time Std. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

highlight the existence of early signs of gait changes like higher gait variability of both temporal and spatial parameters in patients with SCA12.

In our study all the patients exhibited upper extremity tremor (both intention and postural) at baseline with increment in severity at follow-up. The unique manifestation of prominent tremor preceding other symptoms is exclusive in SCA12 compared to other SCAs [1]. Notably, the progress of tremor was not uniform between the two upper extremities of the body. The severity of both intention and postural tremor increased for all the three patients only on the right side and remained the same on the left side (Table 1). Dysarthria in this spectrum of disorder is quite common and all three patients at baseline suffered from speech impairment. There was no worsening of speech at follow-up

The non-motor role of cerebellar degeneration such as considerable differences in cognitive patterns in different types of SCAs (such as type 1, 2, 3) has also been studied [4]. Our study reports a consistent decline of cognition in all three patients as the disease progressed.

To conclude, we present a longitudinal follow-up study in a series of SCA12 patients on discrete gait parameters. Early changes in gait variability were uniformly seen in all our patients. Analyzing such selective gait disturbances before they overtly manifest are likely to act as pre-clinical markers, which detect the early manifestation and quantify disease progression. This might aid in better management of this condition. However, the small sample size of this study is a limitation. Slow progression, lateralized worsening and decline in cognition were other key findings in our study. A future study with a larger sample size is essential to further validate our findings.

Author Contributions

US: Study concept and design, acquisition of data, analysis and interpretation, first draft of the manuscript, critical revision of the manuscript for important intellectual content.

SC: Study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content.

KC: Data analysis and interpretation, critical revision of the manuscript for important intellectual content.

SB, SR: Critical revision of the manuscript for important intellectual content.

BM: Acquisition of data, Critical revision of the manuscript for important intellectual content.

PB: Critical revision of the manuscript for important intellectual content.

Table 2

Comparing objective gait variables between SCA 6^{Pre} (ICARS < 7), SCA 6^{Clin} (ICARS > 10) and SCA 12 (baseline and follow-up). (Gait data of SCA 6 was taken as a historical control from Rochester et al. 2013 [10]).

Variables	SCA 6		SCA12	
	SCA 6 ^{Pre}	SCA6 ^{Clin}	SCA12 ^{Baseline}	SCA12 ^{follow-up}
Age(yrs)	42.33 ± 14.6	61.5 ± 8.5	59.33 ± 4.9	
Sex (M, F)	2M,4F	5M,13F	3M	
ICARS	2.5 ± 0.5	18.8 ± 1.9	32.7 ± 6.7	40.7 ± 9.0
Gait Variables				
Velocity(m/s)	1.50 (1.27, 1.59)	0.95 (0.80, 1.19)	0.72 (0.70, 0.98)	0.66 (0.64, 0.78)
Step Length(m)	0.75 (0.65, 0.80)	0.55 (0.42, 0.66)	0.46 (0.45, 0.57)	0.44 (0.39, 0.47)
Step Time Std(ms)	12.67 (11.14, 16.18)	24.43 (19.02, 38.44)	616.00 (577.50, 623.50)	583.00 (576.00, 605.00)
Step Length Std(m)	0.020 (0.014, 0.025)	0.032 (0.024, 0.041)	0.0284 (0.0281, 0.0338)	0.0688 (0.0610, 0.0692)
Step Time Asymmetry(ms)	3.82 (1.47, 11.26)	3.82 (1.47, 11.26)	18.00 (9.50, 20.00)	29.00 (18.50, 31.00)
Step Length Asymmetry(m)	0.017 (0.004, 0.033)	0.022 (0.007, 0.045)	0.031 (0.021, 0.036)	0.041 (0.035, 0.042)
Step width(m)	0.087 (0.052, 0.101)	0.136 (0.100, 0.193)	0.112 (0.091, 0.124)	0.088 (0.067, 0.110)

Values are presented as mean ± SD or median (quartiles).

HK: Study concept and design, Critical revision of the manuscript for important intellectual content, study supervision.

8. Funding Sources and Conflict of Interest

Institutional research fund of HK was used for this study. The authors declare no conflicts of interest relevant to this work.

9. Financial Disclosures

The authors declare that there are no additional disclosures to report.

CRediT authorship contribution statement

Ummatul Siddique: Conceptualization, Methodology, Data curation, Software, Formal analysis, Writing - original draft, Writing - review & editing. **Supriyo Choudhury:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Koustav Chatterjee:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Simin Rahman:** Data curation, Formal analysis, Writing - review & editing. **Sakhi Bhansali:** Data curation, Writing - review & editing. **Banashree Mondal:** Data curation, Writing - review & editing. **Purba Basu:** Writing - review & editing. **Hrishikesh Kumar:** Conceptualization, Writing - review & editing, Supervision.

References

- [1] A.K. Srivastava, A. Takkar, A. Garg, M. Faruq, Clinical behaviour of spinocerebellar ataxia type 12 and intermediate length abnormal CAG repeats in PPP2R2B, *Brain* 140 (1) (2017) 27–36.
- [2] S. Choudhury, S. Chatterjee, K. Chatterjee, R. Banerjee, J. Humby, B. Mondal, S. S. Anand, S. Shubham, H. Kumar, Clinical characterization of genetically diagnosed cases of spinocerebellar ataxia type 12 from India, *Mov. Disord. Clin. Pract.* 5 (1) (2018) 39–46.
- [3] S.E. Holmes, E. O’Hearn, C.A. Ross, R.L. Margolis, SCA12: an unusual mutation leads to an unusual spinocerebellar ataxia, *Brain Res. Bull.* 56 (3–4) (2001) 397–403.
- [4] K. Bürk, Cognition in hereditary ataxia, *The Cerebellum* 6 (3) (2007) 280–286.
- [5] H. Park, H.-J. Kim, B.S. Jeon, Parkinsonism in spinocerebellar ataxia, *BioMed Res. Int.* 2015 (2015).
- [6] E. Buckley, C. Mazzà, A. McNeill, A systematic review of the gait characteristics associated with Cerebellar Ataxia, *Gait Posture* 60 (2018) 154–163.
- [7] V.B. Leotti, J.J. de Vries, C.M. Oliveira, E.P. de Mattos, G.J. Te Meerman, E. R. Brunt, H.H. Kampinga, L.B. Jardim, D.S. Verbeek, CAG repeat size influences the progression rate of spinocerebellar ataxia type 3, *Ann. Neurol.* 89 (1) (2021) 66–73.
- [8] S. Lord, B. Galna, J. Verghese, S. Coleman, D. Burn, L. Rochester, Independent domains of gait in older adults and associated motor and nonmotor attributes: validation of a factor analysis approach, *J. Gerontol. Series A: Biomed. Sci. Med. Sci.* 68 (7) (2013) 820–827.
- [9] W. Ilg, J. Seemann, M.A. Giese, A. Träschütz, L. Schöls, D. Timmann, M. Synofzik, Towards ecologically valid biomarkers: real-life gait assessment in cerebellar ataxia, *bioRxiv* (2019) 802918.
- [10] L. Rochester, B. Galna, S. Lord, D. Mhiripiri, G. Eglon, P.F. Chinnery, Gait impairment precedes clinical symptoms in spinocerebellar ataxia type 6, *Mov. Disord.* 29 (2) (2014) 252–255.