Spinocerebellar Ataxia 12 Patients have better Quality of Life than Spinocerebellar Ataxia 1 and 2

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Abstract

Background: Spinocerebellar ataxia is a neurodegenerative disease. Information on comparative assessment of quality of life (QoL) among SCAs, particularly SCA 12, is scarce. We aimed to compare health-related QoL in SCA 1, 2 and 12. **Methods:** We conducted a cross-sectional study among individuals with genetically-confirmed SCAs. Ataxia severity was assessed using Brief Ataxia Rating Scale (BARS), independence in activities of daily living (ADL) using Katz index (Katz ADL) and depression using Beck's Depression Inventory-II (BDI-II). QoL was assessed via Short Form Health Survey version 2.0 (SF-36). **Results:** We enrolled 89 individuals (SCA1 = 17, SCA2 = 43, SCA12 = 29; 56% males). Mean age at onset (41.0 ± 11.6 for SCA12 versus 24.9 + 7.0 for SCA1 and 28.8 ± 9.8 years for SCA2) was significantly higher among SCA12. SCA12 had lower BARS (mean score 4.1 ± 4.5 versus 10.6 ± 4.6 for SCA1 and 12.5 ± 4.5 for SCA2). SCA12 scored better on all SF-36 subdomains including Physical (PCS) and Mental Component Summary (MCS) scores. PCS score amongst SCA12 was 44.4 ± 9.0 versus 30.4 ± 9.1 for SCA1 and 33.3 ± 8.9 for SCA2. MCS score for SCA12 was 51.4 ± 11.4 versus 41.8 ± 11.5 for SCA1 and 41.8 ± 11.2 for SCA2. SCA12 had lower mean BDI scores (5.0 ± 6.0) versus SCA1 (9.5 ± 11.6) and SCA2 (10.9 ± 10.3). BARS and BDI emerged as significant predictors of most SF-36 subdomains. **Conclusions:** Our study suggests that despite older age and comparable disease duration, SCA12 patients experience better QoL, less severe depression and ataxia versus SCA1 and SCA2. Severity of ataxia and depression are significant predictors of QoL among the three SCA types.

Keywords: Depression, SF-36, spinocerebellar ataxia, trinucleotide repeats

INTRODUCTION

Spinocerebellar ataxias (SCA) are a heterogeneous group of degenerative disorders with autosomal dominant inheritance characterized by gait ataxia, in association with diverse neuraxial involvement.[1] More than 40 distinct genetic subtypes and 30 genes have been identified.[2,3] Prevalence estimates range from 1 to 4 per 100,000 individuals, with the most prevalent forms of SCA worldwide being SCA 1, 2, 3, 6 and 17.[4] However, the most common forms in India are SCA1, 2, 3 and 12, with the latter occurring in a specific ethnic group. SCA2 and 12 are common SCAs in India.[5,6] Life expectancy in these patients may be shortened by six years up to as much as 29 years.[7] Progression of disease limits independence and increases reliance on a caregiver for activities of daily living.[8] The progressive nature of this condition impacts patients' health-related quality of life (HRQoL). Assessment of health related QoL in SCA patients potentially provides useful clinical information, both in terms of disease progression as well as in evaluation of response to treatment.

Comparisons among different SCA types in terms of QoL are also sparse in literature. However, despite lack of definitive treatment, QoL data is still useful in apprising authorities and clinicians of the impact of such rare diseases on the population and the patient individually. Moreover, although some information of QoL is available on patients with SCA1, 2, 3, 6 and 10, there is no study on QoL amongst SCA12 patients. In the current study, we sought to determine health-related QoL in three different types of SCAs i.e., SCA1, 2 and 12 using the generic 36-item Short Form Health Survey (SF-36). We also aimed to identify association of clinical, demographic and social factors such as age, age at disease onset, disease severity, disease duration, depression and activities of daily living on QoL amongst each of the three SCA types.

METHODS

Study participants

In this cross-sectional study, we enrolled consecutive genetically confirmed SCA1, 2 and 12 patients of both genders >=18 years of age from Ataxia Clinic of a tertiary centre in northern India over 1.5 years. The method for CAG repeats length estimation has been described in our previous study.[9] The study was approved by the institutional ethics committee. Written informed consent was obtained from participants.

Patients under 18 years of age, those with concomitant co-morbidities that could influence assessment of QoL and those not willing to participate were excluded.

Clinical profiles of participants were recorded and detailed clinical examination was done. Data regarding age, gender, age at disease onset and disease duration were collected. Ataxia severity was assessed using Brief Ataxia Rating Scale (BARS). They also underwent evaluation for independence in activities of daily living using Katz index (Katz ADL) and depressive symptoms using Beck's depression inventory-II (BDI-II). QoL was assessed by completing the Short Form Health Survey version 2.0 (SF-36).

Study instruments

Brief Ataxia Rating Scale (BARS)

BARS[10] is an abbreviated version of the modified International Co-operative Ataxia Rating Scale (MICARS) consisting of five subsets: Walking capacity (0-8 points), heel-shin test for decomposition of movements (0-4, scored for each side), finger-nose test for decomposition and dysmetria (0-4, scored for each side), dysarthria test for rate, rhythm and clarity of speech (0-4 points) and anomalies of ocular pursuit (0-2 points). Total score is 30 points with higher scores implying greater severity of ataxia.

Katz Index of independence in activities of daily living (Katz ADL)

Katz ADL[11] contains six items (bathing, dressing, toileting, transferring, continence and feeding) to assess functional status as ability to perform these ADLs independently. Each is assessed on a scale of 0 (dependence) to 1 (independence). A score of 6 indicates full function and 0 indicates complete dependence in ADLs.

Beck depression inventory-II (BDI-II)

BDI-II[12] is a 21-item questionnaire to evaluate severity of depressive symptoms. Each item is scored from 0 (no symptoms) to 3 (severe symptoms) with total scores ranging from 0-63 scale. A total score of 0 to 13 indicates minimal depression; 14 to 19 indicates mild depression; 20-28 moderate depression and 29 to 63 indicates severe depression.

Short form health survey version 2.0 (SF-36)

SF-36[13] is a generic health-related quality of life (HRQoL) scale containing 36 items in 8 domains: Physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role emotion (RE) and mental health (MH). For each subscale, items are coded, summed and transformed into a scale ranging from 0 (worst HRQoL) to 100 (best HRQoL) using a software provided by Optum® outcomes. SF-36 also provides two summary scores: Physical Component Summary score (PCS) and Mental Component Summary score (MCS). PCS represents a combination of PF, RP, BP and GH subscales while MCS represents a combination of VT, SF, RE and MH subscales. Scores are norm based (Mean = 50, SD = 10).

Statistical analysis

Data were recorded on a predesigned proforma and managed on MS Excel spreadsheet. Categorical variables were summarised as frequency and percentage. Continuous variables were summarised as mean ± standard deviation. Chi Square test was used to compare categorical variables amongst the three groups. Demographic characteristics, clinical parameters, SF-36 scores and disease severity scores were compared among SCA1, SCA2 and SCA12 groups using One-way analysis of variance followed by Bonferroni correction in *P* value for post-hoc comparisons if required. Correlations between patient characteristics and health related QoL parameters (SF-36) were calculated using Pearson correlation coefficient. Analysis of covariance was used to estimate marginal mean scores (standard error) adjusted for age, gender, age at disease onset and depression (0-100 scale; low score represents poor QoL). Stepwise multiple linear regression, with probability to enter as 0.05 and probability to remove as 0.01, was used to determine independent relationship of various patient characteristics with quality of life subscales in each of the three types. Statistical analysis was performed using Stata 14.0 statistical software. In this study, *P* value of < 0.05 was considered as statistically significant.

RESULTS

The study included 89 patients with SCA (SCA1 = 17, SCA2 = 43, SCA12 = 29) as shown in Table 1. Males constituted 56% of our participants. The mean age at enrolment ± SD was 29.7 ± 7.5 years, 34.3 ± 10.7 years and 45.7 + 12.3 years for SCA1, SCA2 and SCA12 respectively. SCA12 patients were significantly older than SCA1 and SCA2 patients at presentation (p < 0.05). Mean age at onset ± SD was higher for SCA12 patients, being 41.0 + 11.6 years compared to 24.9 + 7.0 years for SCA1 (p < 0.05) and 28.8 ± 9.8 years for SCA2 patients (p < 0.05). SCA2 patients had longer duration of disease at presentation (5.4 ± 2.8 years) than SCA1 (4.4 ± 2.6 years) and SCA12 (4.0 ± 2.3 years) although the difference was statistically not significant. Patients with SCA12 had significantly lower mean scores (5.0 ± 6.0) on BDI compared to SCA1 who had a score of 9.5 ± 11.6 (p < 0.05) and SCA2 who had a score of 10.9 + 10.3 (p < 0.05). SCA12 patients also scored significantly lower on the BARS with mean score being 4.1 ± 4.5 compared to 10.6 ± 4.6 for SCA1 (p < 0.05) and 12.5 + 4.5 for SCA2 patients (p < 0.05). There was no difference in the three subgroups in Katz ADL score.

In the QoL domains, patients with SCA12 had significantly higher mean scores, representing better QoL, in nearly all domains compared to patients with SCA1 and SCA2 including overall Physical Component Summary score (physical functioning, role-physical and general health) and Mental Component Summary score (social functioning and role-emotional) [Table 2]. PCS score amongst SCA12 patients was 44.4 ± 9.0 compared to 30.4 ± 9.1 for SCA1 (p < 0.05) and 33.3 ± 8.9 for SCA2 (p < 0.05). MCS score among SCA12 patients was 51.4 ± 11.4 compared to 41.8 ± 11.5 for SCA1 (p < 0.05) and 41.8 ± 11.2 for SCA2 (p < 0.05). Bodily pain, vitality and mental health domains were statistically comparable amongst the three SCA subgroups.

Correlation among various patient characteristics and SF-36 domains is shown in Table 3. Age correlated negatively with physical functioning among SCA1 patients and social functioning and role emotional among SCA2 patients. Age at onset correlated negatively with social functioning and role emotional domains for SCA2 alone. Age at onset did not show any correlation with SF-36 domains in SCA1 and SCA12 patients. Disease duration did not show any correlation with SF-36 domains in SCA1 patients. Disease duration showed negative correlation with physical functioning, role physical, general health domains and physical combined score in SCA2 patients. All domains except role physical showed negative correlation with disease duration in SCA12 patients. CAG repeat length did not show

any correlation with SF-36 domains and summary scores in any of the three SCA types.

In ADL score, positive correlation was found in several domains (PF, GH, VT, SF, MH and MCS) for SCA12 patients and in vitality, mental health and MCS in SCA2 patients but no correlation was noted in SCA1. BDI scores demonstrated significant negative correlation with all SF-36 domains in SCA2 patients and for most domains (GH, VT, SF, MH and MCS) in SCA12 patients but no correlation was found in SCA1.

BARS had highest degree of negative correlation with most SF-36 domains and summary scores in SCA12 patients. Except bodily pain and mental health in SCA1 and several domains (RP, BP, GH, SF, MH and PCS) in SCA2 patients, all other domains correlated negatively.

Table 4 shows results of multiple linear regression analysis and it demonstrates independent significant association of various factors (age, age at onset, disease duration, ADL, BDI, BARS and CAG repeats) with QoL subscales including component scores as dependent variables. BARS showed significant negative association with nearly all domains of SF-36 for the three SCA types, particularly for SCA12 in which association was demonstrable with all QoL domains. Similarly, BDI showed significant negative association with nearly all QoL domains, and this association was strongly seen for SCA2 in which all QoL domains associated with

Table 1: Comparison of various patient characteristics amongst three SCA types

Variable	SCA1 (*n*=17)	SCA2 (*n*=43)	SCA12 (*n*=29)
Age (years)	29.7±7.5	34.3±10.7	45.7±12.3[a,b]
Age at disease onset (years)	24.9±7.0	28.8±9.8	41.0±11.6[a,b]
Duration of symptoms (years)	4.4±2.6	5.4±2.8	4.0±2.3
CAG repeats	58.9±8.0	46.2±10.4	52.7±9.5
Activities of Daily Living (ADL) Score	5.1±1.6	5.3±1.6	5.7±1.0
Depression (Beck Depression Inventory) BDI >=14	4 (23.5%)	16 (37.2%)	3 (10.3%)
Ataxia Severity (Brief Ataxia Rating Scale) BARS	10.6±4.6	12.5±4.5	4.1±4.5[a,b]

Values are expressed as mean±SD or frequency (%) a: SCA1 versus SCA12: *P*<0.016 b: SCA2 versus SCA12: *P*<0.016 Comparison between SCA1 and SCA2 was not significant

Table 2: Comparison of quality of life (QoL) subscales (mean + SE) amongst SCA types

SF 36 Subscales	SCA1 (*n*=17)	SCA2 (*n*=43)	SCA12 (*n*=29)
Physical Component Score (PCS)	30.4 (9.1)	33.3 (8.9)	44.4 (9.0)[a,b]
Physical functioning (PF)	15.5 (27.5)	24.6 (26.9)	65.4 (27.2)[a,b]
Role-Physical (RP)	20.4 (34.3)	25.5 (33.6)	54.9 (34.0)[a,b]
Bodily Pain (BP)	66.6 (27.9)	70.5 (27.4)	82.0 (27.7)
General Health (GH)	33.2 (20.3)	37.9 (19.9)	58.4 (20.1)[a,b]
Mental Component Score (MCS)	41.8 (11.5)	41.8 (11.2)	51.4 (11.4)[a,b]
Vitality (VT)	64.8 (23.8)	61.9 (23.3)	77.0 (23.6)
Social Functioning (SF)	36.8 (25.6)	40.8 (25.1)	77.1 (25.4)[a,b]
Role-Emotional (RE)	21.4 (36.4)	31.8 (35.7)	63.5 (36.1)[a,b]
Mental Health (MH)	74.7 (18.0)	71.3 (17.7)	82.9 (17.9)

Estimated marginal mean scores (standard error) adjusted for age, gender, age at disease onset and depression (0-100 scale; low score represents poor QoL) Analysis of covariance, *P* value based on *F* distribution [a]SCA1 versus SCA12: *P*<0.016 (adjusted *P* value for multiple comparisons) [b]SCA2 versus SCA12: *P*<0.016

Table 3: Correlation coefficients between different variables and Health related QOL and patient characteristics (Using SF36)

Variable	SCA Type	N	Physical Component				Mental Component				Combined Scores	
			Physical Functioning	Role Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role Emotional	Mental Health	Physical	Mental
Age	SCA1	17	-0.70*	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-0.73*	n.s.
	SCA2	43	n.s.	n.s.	n.s.	n.s.	n.s.	-0.46*	-0.50*	n.s.	n.s.	n.s.
	SCA12	29	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Age at disease onset	SCA1	17	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	SCA2	43	n.s.	n.s.	n.s.	n.s.	n.s.	-0.42*	-0.43*	n.s.	n.s.	n.s.
	SCA12	29	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-0.16	n.s.	n.s.	n.s.
Disease duration	SCA1	17	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-0.45	n.s.	n.s.	n.s.
	SCA2	43	-0.52*	-0.52*	n.s.	-0.49*	n.s.	n.s.	n.s.	n.s.	-0.55*	n.s.
	SCA12	29	-0.72*	n.s.	-0.63*	-0.79*	-0.72*	-0.66*	-0.52*	-0.74*	-0.70*	-0.66*
CAG repeat length	SCA1	17	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	SCA2	43	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	SCA12	29	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Activities of daily Living	SCA1	17	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	SCA2	43	n.s.	n.s.	n.s.	n.s.	0.46*	n.s.	n.s.	0.57*	n.s.	n.s.
	SCA12	29	0.51*	n.s.	n.s.	0.60*	0.85*	0.58*	n.s.	0.73*	n.s.	0.64*
Depression (Beck Depression Inventory)	SCA1	17	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-0.58
	SCA2	43	-0.51*	-0.47*	-0.56*	-0.63*	-0.72*	-0.53*	-0.46*	-0.83*	-0.49*	-0.71*
	SCA12	29	n.s.	n.s.	n.s.	-0.60*	-0.54*	-0.53*	n.s.	-0.63*	n.s.	-0.62*
Ataxia Severity (BARS)	SCA1	17	-0.79*	-0.77*	-0.42	-0.72*	-0.54*	-0.76*	-0.70*	n.s.	-0.85*	n.s.
	SCA2	43	-0.47*	n.s.	n.s.	n.s.	-0.46*	n.s.	-0.53*	n.s.	n.s.	-0.46*
	SCA12	29	-0.89*	-0.74*	-0.86*	-0.72*	-0.74*	-0.88*	-0.84*	-0.84*	-0.86*	-0.86*

BARS=Brief Ataxia Rating Scale; n.s. = not significant *P<0.006 statistically significant (multiplicity adjusted P value)

BDI. A strong positive association was also seen with ADL for several domains (bodily pain, social functioning, vitality, mental health, MCS) for SCA12 patients. Age, age at onset and disease duration also showed significant association with QoL subscales but to a lesser extent than BARS, BDI and ADL. CAG repeats had significant negative association with general health, mental health and MCS only for SCA1 patients. For QoL domains and component scores, the coefficient of determination ranged from 32 to 92% explaining substantial variation in the QoL subscales.

Discussion

We report HR-QoL among three common SCAs in India (SCA1, 2 and 12) using the SF-36 questionnaire. In our study, patients with SCA12 were significantly older at disease onset than SCA1 and SCA2. Older age at disease onset has been previously described for SCA12. In our previous description of 5 Indian families, mean age at disease onset was 37.2 (range 26-50) years.[14] In another cohort of 21 patients with genetically confirmed SCA12 from eastern India, mean age at onset was even higher (51.33 ± 8.98 years).[5] Negative correlation between age at onset and length of pathological polyglutamine repeats has been definitively demonstrated, although there is substantial variability in age at onset in SCAs as such.[15] However, length of pathological repeats may only contribute 50 to 90% variability in age of onset and there may

be other reasons in SCA12 as well.[15–17] This is also supported by our previous study demonstrating that intermediate length pathogenic repeats did not clearly correlate with age of onset, suggesting that other contributory factors exist.[18]

We observed less severe ataxia amongst SCA12 than SCA1 and SCA2 patients. SCA12 patients have a known propensity to present with action tremors of limbs, tremulous speech and head tremors preceding ataxia.[5,14] The mean ICARS score presented for SCA12 patients by Choudhary *et al*.[5] was 41.2 + 13.8 suggesting stage 2 (of 3) of ataxia. Higher severity of ataxia in this study could be due to much longer disease duration of 9.24 ± 5.1 years among their SCA12 cohort compared to ours.

In our study, all three SCA types exhibited no/mild depression, with SCA12 patients aggregating significantly lower scores compared to SCA1 and 2. Depression prevails in up to 17-26% of SCA patients (including SCA1, 2, 3, 6)[19] and up to 33% of SCA12 patients.[5] Depression is likely associated with the neurodegenerative process in SCAs. In a previous study, depressive symptoms correlated with severity of ataxia.[19,20] However, depression may not be singularly attributable to motor dysfunction. Patients with greater ataxia severity (e.g. SCA1) may have lower depression compared to less ataxic types such as SCA3. Additionally, while ataxia severity worsens, depression scores remain static up to two years.[20] Depression has been determined to correlate with

Table 4: Association of factors with QoL Subscales: Results of multivariate linear regression analysis		
Quality of Life - SF 36 subscale	**SCA Type**	**Adjusted R^2 (in percent)**
Physical Component Summary Score (PCS)	SCA 1	81
	SCA 2	47
	SCA12	81
Physical Functioning (PF)	SCA 1	67
	SCA 2	50
	SCA12	86
Role-Physical (RP)	SCA 1	76
	SCA 2	40
	SCA12	61
Bodily Pain (BP)	SCA 1	40
	SCA 2	32
	SCA12	79
General Health (GH)	SCA 1	83
	SCA 2	52
	SCA12	72
Mental Component Summary Score (MCS)	SCA 1	75
	SCA 2	58
	SCA12	89
Vitality (VT)	SCA 1	60
	SCA 2	57
	SCA12	92
Social Functioning (SF)	SCA 1	60
	SCA 2	39
	SCA12	84
Role-Emotional (RE)	SCA 1	50
	SCA 2	46
	SCA12	77
Mental Health (MH)	SCA 1	60
	SCA 2	70
	SCA12	92

poor functional status and QoL in patients with SCA1, 3 and 6 apart from ataxia progression.[20] Lower scores on BDI-II in our SCA12 patients were also consistent with generally lower scores on BARS.

Although our SCA patients exhibited low scores on BDI-II scale with mean scores lying within normal cut-off, we did not compare these with healthy controls. Similar to our study, overall mean scores in minimal to mild range of severity were observed in patients with Friedreich ataxia in whom depression was assessed using Beck Depression Inventory (BDI).[21] However, these mean scores displayed significantly higher values compared to the general population.

Among SCA1 patients, only age at presentation and ataxia severity correlated with few QoL domains. Despite SCA1 patients having lowest mean age at presentation in our cohort, we found that age correlated with QoL. This is likely to be due to the severity of SCA1, which shows faster progression compared to 2, 3 and 6.[22]

Among SCA2 patients, we found that disease duration correlated with several QoL domains which mainly defined

the PCS. This is probably due to progressive severity of ataxia among SCA2 patients, also evidenced by their high BARS scores. ADL score impacted mainly MCS components, suggesting that functional dependence influences mental aspects of QoL. Disease duration has been previously reported to correlate with greater disease severity, balance problems, and increased functional dependence among SCA2 patients.[23] Depression affected QoL domains among SCA2 in a broad manner in our study. Although depression severity has not been differentially reported to be higher in SCA2, we found a higher proportion among SCA2 compared to SCA1.[19,24]

Interestingly, despite older age at onset among SCA12 patients, this did not impact QoL domains whereas duration of disease did, suggesting that despite later disease onset, its progressive nature does influence QoL. Age less than 34 years is associated with higher scores in vitality and social functioning domains on SF-36 in a previous study among SCA patients.[25] Depression and ataxia severity emerged as significant predictors of QoL domains amongst SCA12 patients despite relatively low mean scores; Hence, even mild depression and ataxia significantly influence QoL.

In our study, Katz ADL score and ataxia severity dominantly accounted for the variance in QoL amongst SCA12 patients. This suggests that functional independence is a dominant contributor towards better QoL in SCA12. Depression, although consistently noted, had lower impact on PCS or MCS scores. BDI contributed strongly to QoL. Hence, patients' perception of QoL is only partially influenced by disease-related physical impairment, but also other factors such as depression, which therefore, must be carefully sought and treated.

There are a few longitudinal and cross-sectional studies among SCA patients which have observed that they perceive poor health as a result of depression, pain and functional impairment, and visual abnormalities.[8,20,25–29] In a large European multicentric study of 526 SCA patients that used Euro-Quality of 5 Dimensions (EQ-5D) to assess QoL, no difference in rating was found between SCA1, 2, 3 and 6 except more frequent pain among SCA3 patients.[27] Unlike the above and other studies, we have employed SF-36 as a tool to measure QoL. SF-36 has been used in one other study amongst SCA patients. In a cross-sectional Spanish study which used the SF-36 in 80 patients with SCA, SF-36 scores correlated with both disease duration and disease severity.[25] In a study from India, among 41 SCA patients of types 1, 2 and 3, mean global score for WHO-QOL (0-100 scale) was 50.3 ± 12.8, although this study did not assess determinants of QoL.[30]

The novelty of our study is that it assesses QoL and its determinants among SCA12 patients in comparison to SCA1 and 2. Our report includes patients who had mild to moderate disease, both in terms of ataxia severity as well as mean disease duration. Despite this, there was significant impairment in QoL although SCA12 patients fared relatively better. We did not evaluate the presence of other movement disorders or non-cerebellar features except depression. A detailed

neuropsychiatric profile was not performed including suicidal ideation which is reportedly increased among SCA patients.

We acknowledge that a comparison among different SCAs is limited by inability to select a comparable disease stage since rates of progression differ. As such, a longitudinal study with a larger cohort will be additionally informative, especially as our sample size is small. Since this is a cross-sectional study, it does not explore evolution of QoL with disease progression and whether these predictive determinants continue to play contributory roles. Additionally, poor QoL is not entirely explained by the factors that we have studied, and socio-demographic factors need to be assessed to more comprehensively explain poor QoL in SCA patients.

CONCLUSIONS

Our study reports that patients with SCA12 experienced better QoL compared to SCA1 and SCA2 patients at similar disease duration despite being significantly older. SCA12 patients showed less severe depression and ataxia than SCA1 and 2. The severity of ataxia and depression emerged as significant predictors of QoL amongst all three SCA types. Longitudinal QoL outcomes in these patients, relative to other SCA types, must be determined in future studies to see if this relative QoL advantage amongst SCA12 patients persists, or gets eclipsed with time.

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Declaration
Permission to use Beck Depression Inventory (BDI II) was obtained from Pearson India Education Services Private Limited.

Ethical compliance statement
The study was approved by the Ethics committee, All India Institute of Medical Sciences, New Delhi (IESC/T-209/2010).

Informed consent
Written informed consent was obtained from all study participants.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Sun Y-M, Lu C, Wu Z-Y. Spinocerebellar ataxia: Relationship between phenotype and genotype-A review. Clin Genet 2016;90:305-14.
2. Shakkottai VG, Fogel BL. Clinical neurogenetics: Autosomal dominant spinocerebellar ataxia. Neurol Clin 2013;31:987-1007.
3. Durr A. Autosomal dominant cerebellar ataxias: Polyglutamine expansions and beyond. Lancet Neurol 2010;9:885-94.
4. Tsuji S, Onodera O, Goto J, Nishizawa M, Study Group on Ataxic Diseases. Sporadic ataxias in Japan--A population-based epidemiological study. Cerebellum Lond Engl 2008;7:189-97.
5. Choudhury S, Chatterjee S, Chatterjee K, Banerjee R, Humby J, Mondal B, *et al*. Clinical characterization of genetically diagnosed cases of Spinocerebellar Ataxia type 12 from India. Mov Disord Clin Pract 2018;5:39-46.
6. Bhanushali AA, Venkatesan R, Das BR. Spinocerebellar ataxias in India: Three-year molecular data from a central reference laboratory. Neurol India 2020;68:86.
7. Schmitz-Hübsch T, Coudert M, Bauer P, Giunti P, Globas C, Baliko L, *et al*. Spinocerebellar ataxia types 1, 2, 3, and 6: disease severity and nonataxia symptoms. Neurology 2008;71:982-9.
8. López-Bastida J, Perestelo-Pérez L, Montón-Alvarez F, Serrano-Aguilar P. Social economic costs and health-related quality of life in patients with degenerative cerebellar ataxia in Spain. Mov Disord 2008;23:212-7.
9. Faruq M, Scaria V, Singh I, Tyagi S, Srivastava AK, Mukerji M. SCA-LSVD: A repeat-oriented locus-specific variation database for genotype to phenotype correlations in spinocerebellar ataxias. Hum Mutat 2009;30:1037-42.
10. Schmahmann JD, Gardner R, MacMore J, Vangel MG. Development of a brief ataxia rating scale (BARS) based on a modified form of the ICARS. Mov Disord 2009;24:1820-8.
11. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. Gerontologist 1970;10:20-30.
12. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
13. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
14. Srivastava AK, Choudhry S, Gopinath MS, Roy S, Tripathi M, Brahmachari SK *et al*. Molecular and clinical correlation in five Indian families with spinocerebellar ataxia 12. Ann Neurol 2001;50:796-800.
15. Tezenas du Montcel S, Durr A, Bauer P, Figueroa K, Ichikawa Y, Brussino A, *et al*. Modulation of the age at onset in spinocerebellar ataxia by CAG tracts in various genes. Brain 2014;137:2444-55.
16. Schöls L, Amoiridis G, Büttner T, Przuntek H, Epplen JT, Riess O. Autosomal dominant cerebellar ataxia: Phenotypic differences in genetically defined subtypes? Ann Neurol 1997;42:924-32.
17. Stevanin G, Dürr A, Brice A. Clinical and molecular advances in autosomal dominant cerebellar ataxias: From genotype to phenotype and physiopathology. Eur J Hum Genet 2000;8:4-18.
18. Srivastava AK, Takkar A, Garg A, Faruq M. Clinical behaviour of spinocerebellar ataxia type 12 and intermediate length abnormal CAG repeats in PPP2R2B. Brain J Neurol 2017;140:27-36.
19. Schmitz-Hübsch T, Coudert M, Tezenas du Montcel S, Giunti P, Labrum R, Dürr A, *et al*. Depression comorbidity in spinocerebellar ataxia. Mov Disord 2011;26:870-6.
20. Lo RY, Figueroa KP, Pulst SM, Wilmot G, Gomez C, Schmahmann J, *et al*. Depression and clinical progression in spinocerebellar ataxias. Parkinsonism Relat Disord 2016;22:87-92.
21. Nieto A, Hernández-Torres A, Pérez-Flores J, Montón F. Depressive symptoms in Friedreich ataxia. Int J Clin Health Psychol 2018;18:18-26.
22. Jacobi H, Bauer P, Giunti P, Labrum R, Sweeney MG, Charles P, *et al*. The natural history of spinocerebellar ataxia type 1, 2, 3, and 6: A 2-year follow-up study. Neurology 2011;77:1035-41.
23. Amarante TRP, Takeda SYM, Teive HAG, Zonta MB. Impact of disease duration on functional status of patients with spinocerebellar ataxia type 2. Arq Neuropsiquiatr 2017;75:773-7.
24. Klinke I, Minnerop M, Schmitz-Hübsch T, Hendriks M, Klockgether T, Wullner U, *et al*. Neuropsychological features of patients with Spinocerebellar ataxia (SCA) types 1, 2, 3, and 6. Cerebellum 2010;9:433-42.
25. Sánchez-López CR, Perestelo-Pérez L, Escobar A, López-Bastida J, Serrano-Aguilar P. Health-related quality of life in patients with spinocerebellar ataxia. Neurologia 2017;32:143-51.
26. Santos LR, Teive HAG, Lopes Neto FDN, Macedo ACB de, Mello NM de, Zonta MB. Quality of life in individuals with spinocerebellar ataxia type 10: A preliminary study. Arq Neuropsiquiatr 2018;76:527-33.

27. Jacobi H, du Montcel ST, Bauer P, Giunti P, Cook A, Labrum R, *et al*. Long-term evolution of patient-reported outcome measures in spinocerebellar ataxias. J Neurol 2018;265:2040-51.

28. Kedar S, Ghate D, Murray EL, Corbett JJ, Subramony SH. Vision related quality of life in spinocerebellar ataxia. J Neurol Sci 2015;358:404-8.

29. Schmitz-Hübsch T, Coudert M, Giunti P, Globas C, Baliko L, Fancellu R, *et al*. Self-rated health status in spinocerebellar ataxia--Results from a European multicenter study. Mov Disord 2010;25:587-95.

30. Mastammanavar VS, Kamble N, Yadav R, Netravathi M, Jain S, Kumar K, *et al*. Non-motor symptoms in patients with autosomal dominant spinocerebellar ataxia. Acta Neurol Scand 2020;142:368-76.