Clinical Characterization of Genetically Diagnosed Cases of Spinocerebellar Ataxia Type 12 from India

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Abstract: Background: Spinocerebellar ataxia type 12 (SCA12) is a rare form of an autosomal-dominant ataxic disorder associated with an expansion of CAG repeat length. Here, we present a large case series of patients with SCA12 and describe a wide range of typical and rare symptoms.

Methods: Twenty-one consecutive patients with genetically proven SCA12 underwent detailed neurological examination. We assessed clinical characteristics using validated rating scales for evaluating motor features in SCA. Nonmotor symptoms and quality of life were assessed using appropriate, validated scales. Correlations of CAG repeat length with both severity score and age of onset were explored.

Results: The mean age of onset was 51 years, and most patients were descendants of a single, endogamous Indian community (Agarwal). Tremor was the most common initial presenting symptom (90%). Hand dystonia was present in 14 of 21 patients, and most patients in the cohort presented with gait disturbance. Neuropsychiatric manifestations were common coexisting features. The CAG repeat length was significantly correlated ($r = -0.760$; $P = 0.0001$) with early age of onset, but not with disease severity. Tremor affected the quality of life in 18 of 21 patients, because they had difficulty in handling liquids.

Conclusions: Tremor was the most common, nonataxic symptom at initial presentation in patients with SCA12. Proximal upper limb tremor, typically with high amplitude and low frequency, can raise a strong diagnostic suspicion. Associated hand dystonia was a common coexisting motor feature. Various nonmotor features were also observed in several cases which require therapeutic attention.

Spinocerebellar ataxia type 12 (SCA12), an autosomal dominant cerebellar ataxia, is associated with a CAG repeat extension mutation in the protein phosphatase 2 regulatory subunit Bβ (*PPP2R2B*) gene at position 32 on the long arm of chromosome (5q32).[1,2] This neurodegenerative disorder was first reported in an American family, and similar cases were also identified subsequently in India, Italy, China, and Singapore.[1,3–14] SCA12 is the second most frequent form of autosomal dominant cerebellar ataxia (16%) in India.[6,9,15–17] Reported Indian cases of SCA12 have been traced back to a common founder endogamous ethnic group, the *Agrawals*, originating from northern India.[15] In a 2005 phenotype-genotype study in eastern India, among 54 families that had autosomal dominant cerebellar ataxias, Sinha identified 12 families that were affected with SCA12.[17] SCA12 was correctly described by Sinha et al. as a "private" mutation, because 11 of those 12 SCA12-affected families belonged to the same ethnic group.[16]

SCA presents as a spectrum of overlapping neurologic symptoms with considerable heterogeneity. SCA12 itself can present commonly with nonataxic symptoms. This makes the clinical

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diagnosis of SCA12 somewhat difficult. Currently, the detection of SCA12 depends on genetic tests based on polymerase chain reaction, although the cutoff number of CAG repeats is disputed; therefore, a confident diagnosis may not be possible in patients who have a borderline repeat length. In addition, the clinical features of SCA12 are not well defined, and there is limited available literature illustrating a complete clinical picture.

We conducted this study in a cohort of 21 patients with genetically diagnosed SCA12 at the Institute of Neurosciences Kolkata Hospital, a referral center in eastern India. Here, we present the clinical characteristics of SCA12 based on the neurologic symptoms presented at onset and during the disease course. The objective was to provide a detailed clinical picture of patients with SCA12 to aid in the correct diagnosis and appropriate medical management. We hope that our precise description of the specific tremor characteristics will prove particularly useful.

Patients and Methods

For this cross-sectional study, we prospectively recruited 21 consecutive patients who had genetically confirmed SCA12. In addition to medical history and clinical examination, all patients were evaluated with validated clinical scales to objectively quantify the degree of motor and nonmotor symptoms. The International Cooperative Ataxia Rating Scale and the SCA Functional Index were used to determine the extent of functional impairment. Severity, loss of function, and disability related to tremor were all estimated using the Fahn-Tolosa-Marin Tremor Rating Scale. The quality of life and functional ability of patients with SCA12 were evaluated using the Quality of Life in Essential Tremor Questionnaire. Cognitive function was estimated using the Mini-Mental State Examination, and dementia-related behavioral symptoms were assessed using the Neuropsychiatric Inventory. Gait impairment and the risk of falls were rated using the Functional Gait Assessment (FGA) and the Falls Efficacy Scale-International (FES-I), respectively. A brief description of the rating scales is provided below. Video S1 recording was performed on individual patients for later assessment.

International Cooperative Ataxia Rating Scale

This scale is mainly administered to quantify the level of functional impairment as a result of ataxia. The subdomains evaluated were postural and gait disturbances, limb ataxia, dysarthria, and oculomotor disorders, with higher scores indicating greater impairment (possible score, 0 to 100).

SCA Functional Index

Three functional measures (8-meter walking time, 9-Hole Peg Test [9HPT], and PATA repetition rate) were used as

quantitative performance measures or "timed tests" for patients with SCA.

Falls Efficacy Scale-International

The FES-I is a 16-item questionnaire of fall-related self-efficacy (10 items). FES-I items are rated according to "how concerned you are about the possibility of falling," using the following responses (score in parentheses): not at all (1 point), somewhat (2 points), fairly (3 points), and very (4 points) concerned. Therefore, the total score ranges from 16 to 64 points. Higher values indicate more concern about falling.

Fahn-Tolosa-Marin Tremor Rating Scale

This is a widely used clinical rating scale to objectively quantify rest, postural, and action/intention tremors. The severity of tremor by body part is estimated on a scale from 0 (none) to 4 (severe). The scale is divided into 3 parts: the first 2 parts relate to location of the tremor and ability to perform motor tasks, and the third part is related to patient-reported functional disability.

Quality of Life in Essential Tremor Questionnaire

The predominant presenting symptom for patients with SCA12 was tremor, so we used this measure as a specific indicator of its impact. The cognitive, emotional, and quality-of-life aspects of SCA were measured with physical, psychosocial, communication, hobbies/leisure, and work/finance-related domains scored using a 5-point scale.

The Neuropsychiatric Inventory

This inventory was developed to characterize the neuropsychiatric symptoms of patients with Alzheimer's disease and other neurodegenerative disorders and also to understand the distress experienced by caregivers due to these symptoms. In total, 10 behavioral areas and 2 neurovegetative areas (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep behavior disorders, and eating disorders) were screened using the Neuropsychiatric Inventory.

Statistical Analysis

Data were analyzed using SPSS version 20 (IBM Corporation, Armonk, NY). Categorical variables are presented as frequencies, and numerical variables are expressed as means ± standard deviations. Associations between 2 numerical variables were evaluated using Pearson's correlation coefficient (r). P values <0.05 were considered statistically significant. The study was

approved by the Institutional Ethics Committee, and participants signed informed consent forms.

Results

The mean age of the patients with SCA12 who participated in this study was 60.57 ± 8.73 years, and the mean age at the onset of symptoms for the cohort was 51.33 ± 8.98 years. Of 21 patients, 20 belonged to the same ethnic group from Northwestern India, and 1 patient originated from Eastern India. The parents of all patients had endogamous but nonconsanguineous marriages. The mean CAG repeat length was 55.56 ± 4.55 repeats (range, 51–62 repeats). Gait abnormality was identified as the most common symptom of SCA12, followed by tremor. The mean duration of tremor was 9 hours per day. The mean scores for rating scales along with demographic and disease-related parameters are presented in Table 1.

A systematic assessment of neurologic signs and symptoms is presented in Table 2. Intention tremor was present in 12 of 21 patients. Rest tremor was noted in 10 patients on application of cognitive load. However, postural tremor was present in 17 patients regardless of cognitive load. We observed orofacial tremor in 3 patients, of which 2 also had lingual tremor. Two patients had voice tremor, and trunk tremor was noted in 5 patients. Head tremor was noted in 13 patients. Detailed descriptions of upper limb tremor characteristics are presented in Table S1.

Three patients had rigidity, and 14 had hand dystonia, whereas bradykinesia was present in 11 patients. Twelve patients had hyperreflexia, and a positive Babinski sign was present in 4 patients. Dysarthria was present in 12 patients, whereas urinary disturbances were noted in 11 patients. All patients had notable gait impairment. Moderate-to-severe unstable gait/deviating gait was observed in 13 patients, and 9 patients presented with moderate-to-severe slower gait, as expected by their age. Fourteen of 21 patients had a history of more than 1 fall in the past year.

TABLE 1 Clinical characteristics and demography

Parameter	Mean ± SD
Age at examination, y	60.57 ± 8.73
Age at onset, y	51.33 ± 8.98
Disease duration, y	9.24 ± 5.10
CAG repeat length	55.56 ± 4.55
ICARS	41.20 ± 13.81
FGA score	13.67 ± 7.91
FES-I score	38.70 ± 15.22
MMSE score	25.95 ± 3.86
QUEST	
Overall QoL score	60.75 ± 22.73
Health status score	56.00 ± 18.96
Duration of tremor, h[a]	9.00 ± 7.20

Abbreviations: SD, standard deviation; ICARS, International Cooperative Ataxia Rating Scale; FGA, Functional Gait Assessment (score range, 30–0); FES-I, Falls Efficacy Scale-International (score range, 64–16); MMSE, Mini Mental State Examination (score range, 30–0); QUEST, Quality of Life in Essential Tremor Score components (score range, 100–0); QoL, quality of life.
[a]Duration is reported in any body part in a normal day. The demographic variables CAG repeat length and severity scores are expressed as mean ± SD values in 21 patients.

TABLE 2 Neurologic signs and symptoms on examination

Clinical Parameter	No. of Patients (%)
Tremor	
Intention tremor	12 (57)
Rest tremor	
With cognitive load	10 (48)
Without cognitive load	8 (38)
Postural tremor	17 (81)
Head tremor	13 (62)
Orofacial tremor	3 (14)
Voice tremor	2 (10)
Cerebellar signs	
Dysmetria	12 (57)
Dysarthria	12 (57)
Dyssynergia	12 (57)
Dysdiadochokinesia	12 (57)
Tandem gait impairment	20 (95)
Mild	8 (38)
Moderate	5 (24)
Severe	7 (33)
Nystagmus	3 (14)
Gait	
Slow gait	9 (43)
Deviating gait	13 (62)
History of >1 fall	14 (67)
Walking aid	4 (19)
Accompanying person	2 (10)
Walking stick and accompanying person	1 (5)
Wheelchair	1 (5)
Pyramidal signs	
Spasticity	6 (29)
Babinski's sign	4 (19)
Hyperreflexia	12 (57)
Extrapyramidal signs	
Rigidity	3 (14)
Dystonia	14 (67)
Chorea	0 (0)
Bradykinesia	11 (52)
Features suggestive of peripheral nerve dysfunction	
Paresthesia	2 (10)
Numbness	1 (5)
Painful cramps	6 (29)
Muscle wasting	0 (0)
Bulbar features	1 (5)
Proprioceptive disturbance	1 (5)
Exteroception	1 (5)
Oculomotor abnormalities	
Saccadic abnormalities	4 (19)
Smooth pursuit abnormalities	10 (48)
Diplopia	2 (10)
Other abnormalities	
Urinary problem	11 (52)
Bowel dysfunction	10 (48)
Fatigue	10 (48)
Cognitive impairment (MMSE)	3 (14)
Executive dysfunction	4 (19)
Psychiatric disorders	14 (67)

Abbreviation: MMSE, Mini-Mental State Examination.
[a]Values shown are the number of individuals observed with a particular clinical sign and the percentage prevalence of that sign in the current sample (n = 21 patients).

The cohort of patients with SCA12 selected for this study belonged to 15 apparently unrelated families. For 7 patients, the mother had a similar illness; whereas, for other 7 patients, the father had a similar illness. In a single case, both parents had tremor-related symptoms.

A detailed psychiatric evaluation of the patients with SCA12 is represented in Figure 1A. The commonly observed
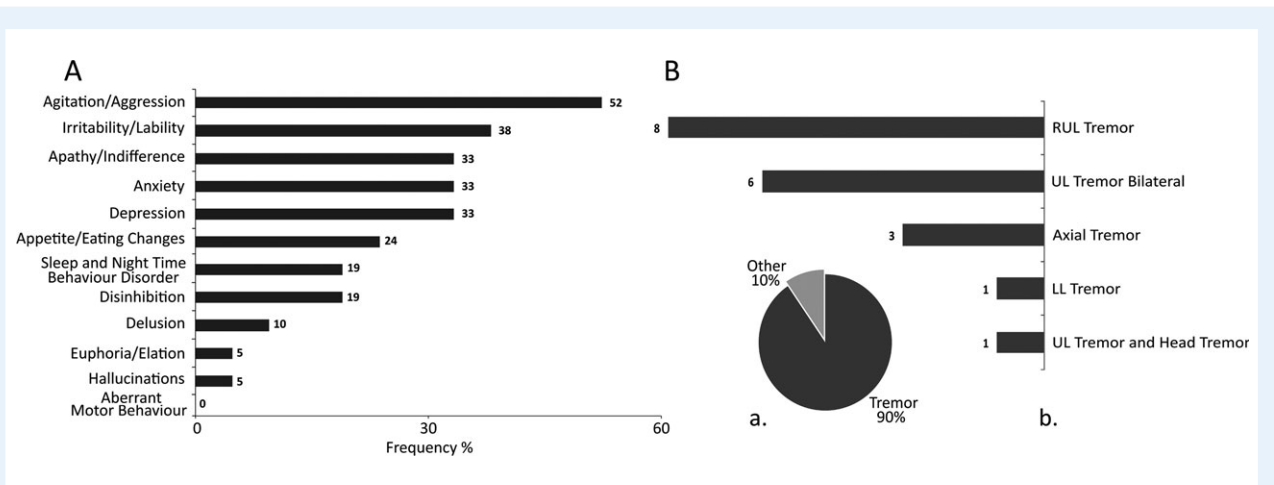
FIG. 1. Psychiatric presentations and initial presenting complaints of spinocerebellar ataxia type 12 (SCA12). (A) More than 1 psychiatric symptom can coexist. (B) Initial presenting complaints of SCA12 include (a) tremor (90%) and other symptoms (dystonia, 5%; gait ataxia, 5%) and (b) tremor at presentation according to anatomic distribution. RUL indicates right upper limb; UL, lower limb, LL, lower limb.

psychiatric symptoms were agitation, irritability, depression, anxiety, and apathy. Hallucinations were noted in 1 patient, and delusions were reported by 2 patients. Appetite changes and sleep behavior disorder were observed in 5 and 4 patients, respectively.

The very first neurologic symptoms at disease onset, as reported by the patients with SCA12, are depicted in Figure 1B. Upper limb tremor was the first major presenting symptom in 15 patients, whereas other initial presenting symptoms included dysarthria and gait abnormality.

Several quality-of-life measures were affected in the majority of our patients. Speech (57%) and writing impairment (95.2%) were the 2 most common impairments. Seventeen patients were unable to maintain day-to-day hygiene, and 18 were unable to handle liquids.

The association between either severity of symptoms or age of onset with CAG repeat length was evaluated. Interestingly, age of onset was significantly correlated with CAG repeat length ($r = -0.760$; $P = 0.0001$) (Table 3). However, the severity of symptoms was not significantly correlated with CAG repeat length. Because SCA12 is a progressive disease, associations between disease duration and disease severity scale scores were also studied and are presented in Table 4. Speech and oculomotor scores were not significantly correlated with disease duration ($P = 0.408$ and $P = 0.109$, respectively); however, we observed associations between disease duration and the scores on the Functional Impairment Scale ($r = 0.617$; $P = 0.004$), FGA scores ($r = -0.477$; $P = 0.029$), and dexterity measures (9HPT: $r = 0.635$; $P = 0.005$). Accordingly, our results suggest that the levels of both functional impairment and deterioration in gait increased progressively alongside disease duration.

TABLE 3 Correlation of CAG repeat length with age of onset and disease severity

Variable	R Value[a]	P Value[b]
Age of onset	−0.760	0.0001
ICARS	−0.203	0.4180
Posture score	−0.210	0.4020
Kinetic score	−0.278	0.2630
Speech score	+0.256	0.3060
Oculomotor score	+0.263	0.2920
FGA score	+0.030	0.9070
SCAFI		
Average 8-m walking speed	−0.197	0.4490
Average 9-hole peg test time, RUL	+0.078	0.7730
Average 9-hole peg test time, LUL	+0.214	0.4270
Average 9-hole peg test time	+0.138	0.6090
Average PATA read-outs in 10 s	+0.241	0.3510

Abbreviations: ICARS, International Cooperative Ataxia Rating Scale; FGA, Functional Gait Assessment; SCAFI, spinocerebellar ataxia functional index; RUL, right upper limb; LUL, left upper limb.
[a]The correlation coefficient (R) was calculated using Pearson's correlation coefficient. An R value of −0.76 indicates a high negative correlation.
[b]P values < 0.05 indicate statistical significance.

TABLE 4 Correlation of duration of disease with disease severity

Variable	R Value[a]	P Value[b]
ICARS	+0.617	0.004
Posture score	+0.508	0.019
Kinetic score	+0.565	0.009
Speech score	+0.191	0.408
Oculomotor score	+0.360	0.109
FGA score	−0.477	0.029
SCAFI		
Average 8-m walking speed	+0.079	0.739
Average 9-hole peg test time, RUL	+0.592	0.010
Average 9-hole peg test time, LUL	+0.666	0.003
Average 9-hole peg test time	+0.635	0.005
Average PATA read-outs in 10 s	−0.237	0.329

Abbreviations: ICARS, International Cooperative Ataxia Rating Scale; FGA, Functional Gait Assessment; SCAFI, spinocerebellar ataxia functional index; RUL, right upper limb; LUL, left upper limb.
[a]The correlation coefficient (R) was calculated using Pearson's correlation coefficient. An R value of +0.617 indicates a moderate positive correlation.
[b]P values < 0.05 indicate statistical significance.

Discussion

SCA12, a mild form of SCA, has a very slow disease progression.[13] Considering the rarity of SCA12 worldwide, only limited studies are available in the literature; therefore, the diagnosis, prognosis, and management of SCA12 remains a daunting task. Taking into account the number of families reported in various studies from India, SCA12 appears to be the second most common type of SCA.[2,9,15,16] Most affected individuals originated from a single, endogamous ethnic group (the Agarwal community). In this study, all but 1 of our patients with SCA12 descended from the Agrawal community. Agarwals are a well-known Indian business community that originated from a small North Indian town called Agroha in the Hissar district of Haryana. These individuals migrated to various parts of India mainly during the Mughal and British era. Currently, they are scattered all over the country, predominantly in business districts.[18] Apart from SCA12 (56% of all SCAs in the Agarwal community), SCA2 (16.7%), SCA3 (3%), SCA7 (3%), and SCA due to an unidentified gene (20%) are also observed in this ethnic group.[19] The Agarwal community also has a higher risk of multiple cardiovascular diseases, such as central obesity, hypertension, lipid abnormalities, and diabetes. This may be associated with low physical activity and high dietary calorie and fat intake.[20] Among neurologic diseases, limb-girdle muscular dystrophy and megalencephalic leukodystrophy with subcortical cysts are relatively more prevalent among the same ethnic group.[21–23]

Depending on the geography of data collection, the prevalence of SCA has varied in different studies from India. SCA2 generally was the most common type in Northern, Eastern, and Western India.[16,24–26] The prevalence of SCA1 was greater in South India, whereas SCA3 was the most common variety among ethnic Bengalis (West Bengal, Eastern India).[27–29]

Patients with SCA12 typically have conspicuous midlife onset of symptoms.[1] A study conducted in patients with SCA12 from 2 Italian families reported that the age at onset was between 45 and 60 years. Although individuals with an American pedigree of German descent had a broader age range of disease onset (ages 8–55 years), most had an onset of symptoms in middle age.[3] Individuals in our current cohort mirror this literature, with an age at symptom onset of 41 to 69 years.[1]

All of our patients with SCA12 carried autosomal-dominant heterozygous mutations, as expected; however, only two-thirds reported a family history of tremor. We suggest that this represents a broad underappreciation of neurologic symptoms and may be a contributing factor in the underreporting of SCA.

Classically, action tremor is the most common initial clinical picture, although its absence does not rule out SCA12. In our study, most patients initially presented with an isolated upper limb tremor; and, in few cases, the tremor was coexistent with an ataxic, slow gait. Interestingly, as reported in the published literature,[17] few of our patients presented with tremor of other body parts (lower limb, trunk, cervical, tongue, and head tremor). Furthermore, in some patients, we observed wing-beating tremor. Tremor intensity increased on cognitive load in several patients (back counting, 10–7 test, etc.). One of our patients did not manifest with any form of tremor, and 2 others presented initially with dysarthria and gait disturbances without a coexisting tremor. However, we note that both patients subsequently developed tremor. Importantly, there is a significant overlap of the symptoms of SCA12 and those of familial essential tremor (ET).[30] It becomes easier to differentiate ET from SCA12 when patients with SCA12 develop frank ataxia and dysarthria later in their disease course; however, this evolution may take years or even decades. Consequently, there are published reports of SCA12 misdiagnosed as ET.[30] In this context, tremor in our current cohort had some odd features that made it different from tremor in ET. The tremor in patients with SCA12 was often slower than that in patients with ET and had higher amplitude. The proximal component was prominent, and the tremor often assumed a wing-beating appearance (Video S1). The tremor frequently was exacerbated when patients were asked to flex their elbows with arms in an outstretched position, so that their hands were closer to the chest (Video S1). Clinicians should actively look for SCA12 when a patient presents with tremors that have the above-mentioned characteristics, especially in the setting of a positive family history in individuals from the Agarwal community.

Because of the presence of hand dystonia in the majority of patients, there was an inclination to consider the tremor in SCA12 as dystonic in origin. However, this assumption was difficult to substantiate, because the coexisting dystonia was be quite subtle and was located exclusively to the distal forearm, whereas the tremor also was proximally prominent. On the basis of our clinical experience of following more than 50 patients with SCA12 patients, we are in favor of considering the tremor in SCA12 as a combination of ataxic, dystonic, and postural tremor unrelated to ataxia or dystonia. However, further neurophysiological evaluation will be required to qualify this statement.

SCA12 may also be mistaken for other forms of SCA.[31] We have highlighted that upper limb tremor is the typical presenting clinical manifestation of SCA12 at disease onset and can differentiate SCA12 from other SCA disorders.[3,17,32] In 2003, Holmes et al. also mentioned the possibility of early and prominent action tremor as a differential feature in patients with SCA12 that gradually progresses to ataxia as well as other cerebellar and cortical signs.[33]

Dystonia was present in the majority of our patients with SCA12, many of whom exhibited hand dystonia alongside tremor. Interestingly, 1 patient also had cervical dystonia. This coexisting feature appears to be quite significant, because the presence of coexisting dystonia can be a diagnostic indicator for SCA12. The concurrent presence of cervical dystonia in a patient with SCA12 also was reported by Ganos et al.,[34] who documented dystonic arm posturing with dystonic tremor.

In approximately one-half of our patients, dysmetria, dyssynergia, and dysdiadochokinesia of the upper limbs were present. All of our patients reported gait abnormality, and most had a significant history of falls. Previous studies have also reported similar motor deficits.[35] Cerebellar signs in the form of

dysmetria, intention tremor, and gait ataxia were also reported by Sinhal.[17] Mild gait instability was noted in the SCA12-affected Italian families; and ataxic, broad-based gait was reported in a member of the American cohort.[36] Difficulty with tandem walking was described in a previous case report by Kalia et al.[37]

Extrapyramidal features of both hypokinetic and hyperkinetic disorders were noted in our cohort (11 patients presented with bradykinesia). Parkinsonian features, such as mild bradykinesia, upper limb rigidity, and postural anteroflexion, also were commonly reported in the American SCA12 cohort.[3] In addition, consistent with a previous report from India, 10 of our patients had rest tremor.[17]

Previously, psychiatric disturbances were documented in some selective cohorts of patients with SCA12[3,5,9,13,31] but were absent in 2 Italian SCA12-affected families.[13] In our study, we documented a detailed neuropsychiatric profile, which showed that psychiatric symptoms were indeed present: agitation/aggression, depression, irritability, anxiety, and apathy/indifference were among the most common psychiatric symptoms. We also observed patients with hallucinations and delusions. Sleep behavior disorder and appetite changes were noted in a few patients with SCA12; however, the concurrent presence of these psychiatric and motor symptoms is most relevant for the diagnosis of SCA12.

We observed that activities of daily living were impaired in our cohort. Over one-half of patients reported difficulty while writing and liquid handling in addition to other motor tasks, including maintaining mouth hygiene, dressing, and using a telephone or computer. To precisely estimate fine motor skills and hand dexterity, we performed the 9HPT. We observed that the mean time to complete the task was significantly longer compared with age-matched and sex-matched normative data from healthy volunteers.[38] In previous studies, action tremor resulted in difficulties performing fine motor tasks (such as writing) and activities requiring gross motor coordination (such as attempting to hold and purposefully manipulate objects like a cup).[36]

The name of this disease, as already known, cannot fully justify its anatomic origin. Patients often present with clinical features that result from the involvement of cortical areas, basal ganglia, and brainstem. Thus we observed smooth pursuit abnormality, saccadic abnormality, lid retraction, and diplopia in several study participants. In a previous study, cranial nerve abnormalities, such as horizontal nystagmus, slow saccades, and broken pursuit, were identified in SCA12-affected populations.[36] Facial myokymia was reported from India in a small proportion of patients with SCA12, but none of our patients had this feature.[36] Pyramidal signs were present in some patients in the form of hyperreflexia, spasticity, and a positive Babinski sign. Brisk deep-tendon reflexes also were noted in patients with SCA12 from the American, Indian, and Italian cohorts.[36] Extensor plantar response, dystonia, painful cramps, memory loss, and poor comprehension have been reported among SCA12-affected Indian patients with advanced-stage of disease.[17]

Neuropathologic investigations in patients with SCA12 indicate that multiple brain regions are affected, with changes most evident in the cerebral cortex and cerebellum.[39] Many neurologic symptoms from our clinical description reflect an even wider neural involvement and support a broad pathologic basis to SCA12. The dopaminergic pathway may be implicated in patients with SCA12, because parkinsonian features were observed in greater than 50% of our cohort. However, this cannot be stated emphatically, because dopamine transporter reuptake scans were not obtained from these patients. In our clinical practice, we use levodopa (L-dopa) during the clinical course of patients with bradykinesia, and the responses were inconsistent. Interestingly, 2 patients from the current cohort had long-term improvement in bradykinesia and gait on L-dopa therapy. It is unclear whether this improvement was related to dopaminergic involvement in patients with SCA12 who responded to L-dopa or was caused by coexisting Parkinson's disease.

There is ambiguity regarding the diagnostic significance of the expansion length of CAG triplets within the *PPP2R2B* gene, because the boundary between the normal and mutated allele is not yet set.[3,5,8,9,31,36,40,41] The diagnostic CAG repeat length for our patients with SCA12 was 56 (range, 51–62 CAG repeats).[42] Srivastava et al. sought to clarify the relevance of CAG codon repeat length for the clinical phenotypes.[32] Those authors found no differences in neurologic symptoms between 18 patients with SCA12 who had 43 to 50 CAG repeats and 9 patients with SCA12 who had >51 CAG repeats.[32] Furthermore, the white matter changes in patients with SCA12 seem to have no correlation with disease severity.[32]

The mechanism by which the mutation of CAG repeat expansion leads to SCA12 has not been deciphered.[43,44] It is possible that there a toxic gain-of-function effect can be attributed to elevated expression of *PPP2R2B* and this the CAG repeat length might correlate with SCA12 disease severity or an earlier onset of symptoms. To test this hypothesis, we evaluated the correlation of CAG repeat length with severity scale scores of SCA12 and onset age. Our study demonstrates that the age of onset is significantly correlated with CAG repeat length. However, we also observed that the severity of symptoms had no significant correlation with the CAG repeat length.

Posture and kinetic scores were associated significantly with disease duration. Furthermore, gait patterns progressively deteriorated over time, as reflected by the association between FGA scores and disease duration. In addition, speech and oculomotor functions were not correlated significantly with disease duration and thus are unreliable markers of progression.

Currently, a significant overlap between different types of SCA is a hurdle for the clinically based diagnosis. For the first time, this study attempts to establish a characteristic phenotype of SCA12 by identifying and grouping both common and atypical symptoms of SCA12 in a large cohort. Current treatment for SCA12 is designed to provide symptomatic relief to ET-like action tremor.[36] Our findings provide insight for medical professionals and will help broaden their horizon when treating patients who have SCA12, particularly with regard to psychiatric symptoms. With the continued accumulation of clinical

information, the field can progress with a more certain diagnostic pathway, increasingly novel research, and the ability to offer patients more holistic and complete management.

Author Roles:

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

    S.Cho.: 1A, 1B, 1C, 2A, 2B, 3A, 3B

    S.Cha.: 1A, 1B, 1C, 2A, 2B, 3A, 3B

    K.C.: 1C, 3B

    R.B.: 1B, 1C, 3B

    J.H.: 3B

    B.M.: 1C, 3B

    S.S.A.: 1C, 3B

    S.S.: 1C, 3B

    H.K: 1A, 1B, 1C, 2C, 3B

Disclosures

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Supporting Information

A video accompanying this article is available in the supporting information here.

Table S1. Detailed descriptions of the individual upper-limb tremor characteristics of the study cohort.

Video S1. Asymmetrical postural tremor is evident in the initial 0 to 11 seconds of the video. The tremor involved predominantly the wrist and was of high amplitude and low frequency. In the later part of the video (12–17 seconds), very-high-amplitude, proximal tremor of the arm resembling a wing-beating appearance was noted. Still later (18–24 seconds), the wrist tremor worsened with the addition of load. The combination of slow, asymmetrical, high-amplitude wrist tremor, along with high-amplitude, proximal tremor, was commonly seen in our cohort of patients with SCA12.