Original Article

Spinocerebellar ataxia type 6 in eastern India: Some new observations

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Abstract

Introduction: Spinocerebellar ataxias (SCAs) are hereditary, autosomal dominant progressive neurodegenerative disorders showing clinical and genetic heterogeneity. They are usually manifested clinically in the third to fifth decade of life although there is a wide variability in the age of onset. More than 36 different types of SCAs have been reported so far and about half of them are caused by pathological expansion of the trinucleotide, Cytosine Alanine Guanine (CAG) repeat. The global prevalence of SCA is 0.3-2 per 100,000 population, SCA3 being the commonest variety worldwide, accounting for 20-50 per cent of all cases, though SCA 2 is generally considered as the commonest one in India. However, SCA6 has not been addressed adequately from India though it is common in the eastern Asian countries like, Japan, Korea and Thailand. **Objective:** The present study was undertaken to identify the prevalence of SCA6 in the city of Kolkata and the eastern part of India. **Materials and Methods:** 83 consecutive patients were recruited for the study of possible SCAs and their clinical features and genotype were investigated. **Results:** 6 of the 83 subjects turned out positive for SCA6, constituting therefore, 13.33% of the patient pool. **Discussion:** SCA6 is prevalent in the eastern part of India, though not as frequent as the other common varieties. **Conclusions:** Further community based studies are required in order to understand the magnitude of SCA6 in the eastern part, as well as in other regions of India.

Key Words

Eastern India, SCA6, Spinocerebellar ataxia

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Introduction

Spinocerebellar ataxias (SCAs) are hereditary, autosomal dominant progressive neurodegenerative disorders showing clinical and genetic heterogeneity.[1] SCAs are usually manifested clinically in the third to fifth decade of life, although there is wide variability in the age of onset. More than 36 different types of SCAs have been reported so far and about half of them are caused by pathological expansion of the trinucleotide, cytosine alanine guanine (CAG) repeat. The global prevalence of SCA is 0.3-2 per 100,000 population,[2] SCA3 being the commonest variety worldwide, accounting for 20-50% of all cases, though SCA2 is generally considered the commonest one in India.[3] The prevalence of SCAs varies significantly depending on race, place of birth, and the founder effect. One study conducted by Subramony *et al*.[4] showed that it was in the range of 1-2 per 100,000 population, whereas another study carried out by Rengaraj *et al*., in two villages populated by ethnic Tamils, indicates that the prevalence is high, at 7.2%.[5] Interest in the field of inherited ataxias in India has been kindled by the cardinal works of Wadia *et al*. over a period of about three decades,[6,7] and a number of other workers from India later reported the phenotype and genotype in various SCAs

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in their studies and showed that the clinical features and genotype varied in different geographical areas.[8-15]

In India, the SCA6 mutation is not common and Gangopadhyay *et al*. reported the first case from Kolkata.[16] Khadilkar *et al*.,[14] reported two patients of SCA6 from Mumbai, a metropolitan, multiethnic city in the western part of India. The objective of the present study is to identify the clinical profile and genetic pattern of SCA6 patients as seen in a tertiary care center in Kolkata, eastern India.

Materials and Methods

This prospective study was carried out at Bangur Institute of Neurosciences, a tertiary referral center in Kolkata. We selected patients from the general outpatient department and they were sent to the neurogenetic clinic. Eighty-three consecutive cases of suspected SCAs were included for genetic study after history taking, analysis of family pedigree, and clinical examination. The clinical examination was carried out by senior neurologists and the findings were recorded in the structured *pro forma* of the neurogenetic clinic. Ethical clearance for the above study was obtained from the institutional ethical committee governed by Indian Council of Medical Research (ICMR) guidelines, and written consent from the patients was obtained before the genetic study.

The inclusion criteria were cases with progressive degenerative cerebellar ataxia, familial or nonfamilial, who were negative for any known metabolic defect. In familial cases, one or more than one member had ataxia other than the proband. Nonfamilial or sporadic cases were individuals with features of primary degenerative cerebellar ataxia without any family history of similar illness. Sporadic cases could be the manifestation of new mutants, skipped generations in autosomal dominant inheritance pattern, or possible unreliable family history about previous generations.

Patients with metabolic, toxic, nutritional, infective, neoplastic, vascular, and alcohol-related degeneration were excluded. Clinical assessment of eye movements in different gazes was done and slow saccades were recognized when eyes moved in a particular gaze taking more than one jump. Slit lamp examination was done in all patients for the presence of Kayser-Fleischer rings and neuroimaging of the brain was performed in all patients. Routine blood biochemistry including blood glucose, lipid profile, thyroid profile, and serum ceruloplasmin were performed in all cases. Serum lactate and serum vitamin E level were performed in selected cases in order to exclude progressive ataxia of known metabolic origin. Electrophysiological evaluation, including nerve conduction study, was done in all cases.

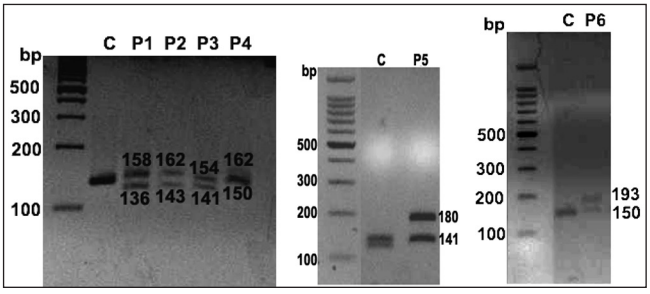

Figure 1: 4% agarose gel electrophoresis pattern of SCA6 are shown with a 100 bp DNA ladder as reference, Lane 1 is DNA ladder, Lane 2 is control in all the figures. (a) Lanes 3, 4, 5, 6 are patient numbers 1, 2, 3, 4 respectively; patients 1 and 2 were siblings (b) Lane 3 is patient number 5 and (c) Lane 3 is patient number 6
C = Control, P = Patient, No. of CAG repeats = bp in gel - 102

Molecular genetic study

Method

1. *Blood sample*: A 5 mL venous blood sample was collected from each patient and preserved in ethylenediaminetetraacetic acid (EDTA) at 20°C
2. *For DNA isolation*: Venous blood, 2× lysis buffer, 1× lysis buffer, 10% sodium dodecyl sulfate (SDS), proteinase K, phenol, chloroform, chilled ethanol, Tris-EDTA buffer
3. *For polymerase chain reaction (PCR):* DNA sample, distilled water, PCR buffer, $MgCl_2$, deoxynucleotide triphosphates (dNTPs), forward primer, reverse primer, Taq polymerase

No.		Sequence (5→3)
1	Forward Primer	CACGTGTCCTATTCCCCTGTGATCC
2	Reverse Primer	TGGGTACCTCCGAGGGCCGCTGGTG

DNA was isolated from the blood samples by phenol chloroform method and stored at 20°C. PCR amplification was carried out in a final reaction volume of 25 µL containing ~100 ng of genomic DNA, 1× PCR buffer, 2 mM $MgCl_2$, 0.2 mM dNTPs, 10 pmol forward primer, 10 picomole reverse primer and the volume was adjusted with distilled water. It is a "hot start" process. Taq polymerase (1.25 units) was added after 3 min incubation at 95°C and subjected to 30 cycles of amplification (95°C for 30 s, 65°C for 30 s, and 70°C for 30 s). The final extension was 72°C for 10 min. PCR products were electrophoresed on 4% agarose gel and visualized under ultraviolet (UV) by a gel documentation system (BIO-RAD) with reference to 100 bp DNA ladder [Figure 1].

Results

We analyzed the genotypes of 83 clinically suspected cases of SCAs for SCA1, SCA2, SCA3, SCA6, and SCA12. Forty-five cases were genetically positive for the SCAs mentioned above, and among these cases we found 6 cases of SCA6. Family history, demography, clinical and investigative parameters, and the results of genetic analysis of SCA6 patients are shown in Table 1, while the relative frequency of different SCAs in India and abroad are shown in Tables 2 and 3.

A 102 bp flanking region is present in the sequence of DNA that we amplified with the primer. Only a crude approximation of the CAG repeats could be done by this method and this is the only way of determining the repeat numbers with the kind of facilities we have. The results are correlated with the clinical findings.

Discussion

The initial symptoms of SCA6 are unsteadiness of gait and imbalance. As the disease progresses, incoordination of limbs

Table 1: Demographic, clinical and investigative parameters of the study patients with SCA 6

	Case-1	Case-2	Case-3	Case-4	Case-5	Case-6	%
Sex	M	M	M	F	F	M	M:F = 2:1
Family history	P	P	–	–	P	–	50 %
Age at presentation (Yrs)	50	63	42	33	56	62	Mean 51
Age Of Onset (Yrs)	45	60	40	29	51	59	Mean 47.33
Duration of illness(Yrs)	5	3	2	4	5	3	Mean 3.67
CAG repeat length	18	22	21	21	30	25	Mean 22.83
Gait ataxia	P	P	P	P	P		100 %
Dysarthria	P	–	–	–	P	P	50 %
Slow saccades	P	P	–	P	–	–	50 %
Nystagmus	–	P	P	P	P	P	83.33 %
Titubation			P				16.67 %
Dysdiadochokinesia	P	–	P	–	P	P	66.67 %
Dysmetria	P	P	P	P	P	–	83.33 %
Cerebellar tremor	P	–	–	P	–	–	33.33 %
Impaired finger nose finger test	P	P	P	P	P	P	100 %
Impaired heel knee keel test	P	P	P	P	P	P	100 %
Tandem gait	P	P	P	P	P	P	100 %
Positive Babinski sign	–	–	–	P	–	–	16.67 %
Parkinsonian features	–	–	–	–	–	–	–
Generalised hyporeflexia	–	–	–	–	–	–	–
MRI Features (Cerebellar atrophy)	–	P	P	–	P	P	66.67 %
Nerve Conduction Study(SNAP reduced)	–	–	P	P	–	–	33.33 %

M = Male, F = Female, P = Present

and tremors are almost invariably present. Diplopia and other visual disturbances occur in about 50% of patients, and in later stages dysphagia is common. SCA6 is a CAG triplet repeat disease in the human α1A voltage-dependent calcium channel subunit gene (CACNL1A4 gene) and the repeat exceeds 19 in number. This gene has two splice forms, Q and P types, and polyglutamine coding CAG expansion occurs in the P form. This form is expressed profusely in the cerebellum where it is localized in the Purkinje cells of the cerebellum, and this leads to early apoptotic cell death.[17,18] Neuropathological examination shows Purkinje cell loss, predominantly in the cerebellar dorsal vermis.

SCA6 is frequent in Korea,[19] Japan,[20] and Taiwan;[21] it is relatively less common among the Chinese and the Caucasians.[22,23] In India, it is rare and Basu *et al*.[10] reported the first case of SCA6 from Kolkata, West Bengal in a 56-year-old female subject who presented with ataxia, dysarthria, and nystagmus. Khadilkar *et al*.[14] reported 2 patients from Mumbai and they found dysarthria, dysdiadochokinesia, dysmetria, and impaired heel-knee test as the predominant features in both the patients, while parkinsonian features were present in 1 subject. None had hyporeflexia or slow saccades, which are notable features of other varieties of SCA, particularly SCA2. Thus, only 3 cases of SCA have been reported from the eastern and the western parts of India so far.

We have found 6 (13.33%) patients of SCA6 in this study in eastern India from among 83 consecutive cases of SCAs. The age at onset varied 45-60 years (mean 47.33 years) and the mean duration of illness was 3.67 years (range 2-5 years). Zhuchenko *et al*.[24] from the USA reported 8 unrelated families, presenting predominantly with mild and slowly progressive cerebellar ataxia, dysarthria, nystagmus, and mild vibratory and proprioceptive sensory loss. Magnetic resonance imaging (MRI) showed isolated cerebellar atrophy and genetic study confirmed the mutation in the CACNL1A4 gene. Jiang *et al*.,[22] reported 13 patients (4 families) of SCA6 from mainland China and observed ataxia in all cases, nystagmus in 12 (92.3%), slow saccades in 13 (100%), ophthalmoplegia in 2 (15.4%), and hyporeflexia in 5 (38.5%) patients. Schöls *et al*.,[25] studied 9 German families where the mean age at onset was 52 years (range 30-71 years) and the mean duration of age was 11 years. Cerebellar signs were prominent, gait ataxia being the initial symptom in all patients, and the other features were external ophthalmoplegia, spasticity, peripheral neuropathy, and parkinsonism. Similar results were replicated in the works of Ishikawa *et al*.,[26] Gomez *et al*.,[27] and Fukutake *et al*.[28] Takiyama *et al*. conducted a study on a Japanese family that included 13 persons with SCA6 in five generations, where the CAG repeat was 21 in length. This family showed some characteristic clinical and genetic features, including apparent lack of genetic anticipation with a stable CAG repeat size over generations and downbeat nystagmus and diabetes mellitus in some of the patients.[29] However, Zhuchenko *et al*. noted a positive correlation between the repeat numbers of earlier onset of the disease, while Takahashi *et al*. in their retrospective analysis of 140 patients observed an inverse correlation between the age of onset and the length of the expanded allele.[24,30] Matsuyama *et al*.,[2] analyzed 60 SCA6 individuals from 39 Japanese families and found that the CAG repeat length was inversely correlated with age of onset, and a similar observation was reported by Ishikawa *et al*.[31] Riess *et al*. observed CAG repeat expansion in four sporadic cases as well.[32] Van de Warrenburg *et al*. used statistical analysis to examine the relationship between the age

Table 2: Demographic, clinical and investigative parameters of the study patients with SCA

	SCA-1 (*n* = 13)	SCA-2 (*n* = 18)	SCA-3 (*n* = 7)	SCA-6 (*n* = 6)	SCA-12 (*n* = 1)	Undetermined (*n* = 38)
Positive family history	9	15	6	3	0	21
N=83	13	18	7	6	1	38
Male /Female	8/5	15/3	4/3	4/2	1/0	28/10
Mean Age at presentation (Yrs)	43.62	33.94	42.29	51.00	68	43.92
Range(Yrs) of Age at presentation	26-58	16-48	27-57	33-62	–	16-68
Mean Age Of Onset (Yrs)	38.46	29.55	38.43	47.33	60	39.40
Range(Yrs) of Age Of Onset	19-54	14-44	26-55	20-59	–	14-60
Mean Duration of illness(Yrs)	5.15	4.39	3.86	3.67	8	4.52
Gait ataxia	13 (100%)	18 (100%)	7 (100%)	6 (100%)	1 (100%)	38 (100%)
Dysarthria	13 (100%)	17 (94.44%)	4 (57.14%)	3 (50%)	1 (100%)	33 (100%)
Slow saccades	7 (53.85%)	17 (94.44%)	4 (57.14%)	3 (50%)	0	18 (47.37%)
Nystagmus	2 (15.38%)	1 (5.56%)	6 (85.71%)	5 (83.33%)	–	13 (34.21%)
Titubation	1 (7.67%)	–	–	1 (16.67%)	–	3 (7.89%)
Dysdiadochokinesia	11 (84.62%)	14 (77.78%)	4 (57.14%)	4 (66.67%)	1 (100%)	32 (84.21%)
Dysmetria	12 (92.30%)	13 (72.22%)	5 (71.43%)	5 (83.33%)	1 (100%)	33 (86.84%)
Cerebellar tremor	4 (40%)	6 (40%)	1(14.28%)	2 (33.33%)	1 (100%)	6 (15.79%)
Impaired finger nose finger test	13 (100%)	18 (100%)	7 (100%)	6 (100%)	1 (100%)	38 (100%)
Impaired heel knee keel test	13 (100%)	18 (100%)	7 (100%)	6 (100%)	1 (100%)	38 (100%)
Tandem gait	13 (100%)	18 (100%)	7 (100%)	6 (100%)	1 (100%)	38 (100%)
Positive Babinski sign	8 (61.53%)	4(22.22%)	4 (57.14%)	1 (16.67%)	–	8 (21.05%)
Parkinsonian features	–	–	–	–	–	–
Generalised hyporeflexia	–	5 (27.78%)	–	–	–	4 (10.53%)
MRI Features	Cerebellar atrophy - 9 (69.23%)	Hind brain atrophy - 15 (83.33 %)	Cerebellar atrophy -5 (71.43%)	Cerebellar atrophy -4(66.67%)	Cerebellar atrophy - 1 (100%)	
Nerve Conduction Study	Sensory axonal neuropathy (SNAP reduced-4, absent- 1)	Sensory axonal neuropathy (SNAP reduced-2, absent-5)	Sensory axonal neuropathy (SNAP reduced- 2)	Sensory axonal neuropathy (SNAP reduced-2)	Not done	
CAG repeat length range	45-86	37-65	46-93	18-30	64	-

Table 3: Relative frequencies of different SCAs in India and abroad

	Number of subjects/ families	SCA 1 (%)	SCA 2 (%)	SCA 3 (%)	SCA 6 (%)	SCA 7 (%)	SCA 10 (%)	SCA 12 (%)	Unknown SCA (%)
Saleem *et al.*[8] (North)	42 (families)	3	10	2	0	0	NA	NA	24
Shrivastava *et al.*[25] (North)	77 (families)	NA	NA	NA	NA	NA	NA	5	NA
Basu *et al.*[9] (East)	57 (families)	6 (10.5)	10 (17.5)	4 (7.0)	1 (1.8)	0	NA	NA	36 (63.2)
Chakravarty *et al.*[10] (East)	14 (families)	2 (14.3)	4 (28.6)	5 (35.7)	NA	0	NA	NA	3 (21.4)
Sinha *et al.*[13] (East)	28 (families)	4 (14.3)	16 (57.1)	0	NA	0	NA	0	8 (28.6)
Krishna *et al.*[19] (South)	105 (families)	34 (32.4)	24 (22.9)	15 (14.3)	NA	NA	NA	NA	32 (30.4)
Wadia *et al.*[7] (West)	51 (families)	NA	14	NA	NA	NA	NA	NA	NA
Khadilkar *et al.*[12] (West)	30 (subjects)	1 (3.3)	10 (33.6)	1 (3.3)	2 (6.7)	0	NA	0	16 (53.3)
Jiang *et al.*[24]	120 (families)	NA	NA	13	83	NA	NA	NA	NA
Lee *et al.*[21] (Korea)	253 (subjects)	6	17	15	10	4	NA	NA	NA
Teive *et al.*[22] (Brazil)	104 (families)	4	12	101	1	5	27	NA	123
Present study (East)	83 (subjects)	13	18	7	6	0	0	1	38

at onset and number of expanded triplet repeats from a Dutch-French cohort of 802 patients with SCA1, SCA2, SCA3, SCA6, and SCA7. The size of the expanded repeat explained 66-75% of the variance in age at onset for SCA1, SCA2, and SCA7, but less than 50% for SCA3 and SCA6.[33]

In an attempt to identify the phenotypic characteristics, Schöls *et al*. compared the clinical, electrophysiological, and MRI findings of genetically proven cases of SCA6 and observed that they presented with predominantly cerebellar syndrome, the age of onset was more than 55 years of age, and the MRI scan showed pure cerebellar atrophy.[34] Oculomotor function studies revealed that all the patients had gaze-evoked nystagmus and a substantial number presented with rebound nystagmus. Spontaneous downbeat nystagmus was another consistent feature, and saccadic velocity was within normal limits.[35,36]

In a family initially classified as autosomal dominant cerebellar ataxia of unknown genotype, Jodice *et al*. found an intergenerational allele size change in the CACNA1A gene, showing that a CAG20 allele was associated with the phenotype of episodic ataxia type 2, while a CAG(25) allele was linked to progressive cerebellar ataxia. These results suggested that episodic ataxia 2 and SCA6 are identical disorders with a high phenotypic variability, which is at least partly related to the number of repeats.[37] The work of Sinke *et al*. revealed that some patients with ataxia had episodic nausea and headache, and they concluded that there might be some overlap between SCA6, episodic ataxia, and familial hemiplegic migraine.[36] Alonso *et al*., in a study of 17 patients in a family over four generations, observed that all of them suffered from hemiplegic migraine and/or SCA6. All the patients had a common mutation in the CACNA1A gene, and the researchers suggested that episodic ataxia 2, SCA6, and familial hemiplegic migraine were possibly the same disorder with diverse phenotypic variability.[38]

SCA6 accounts for about 10% of the autosomal dominant cerebellar ataxia cases in Germany[32] and approximately 11% of all Dutch families.[36] Soong *et al*. observed that among Taiwanese patients SCA6 constituted 10.8% of familial cases and 4.1% of sporadic cases.[21] In the Korean population, 19% of cases of SCA belonged to SCA6.[19] Importantly, among 113 Japanese families from the island of Hokkaido suffering from various varieties of SCA, Basri *et al*. found that SCA6 was the most common form, identified in 35 (31%) families.[39]

Conclusion

We have revealed the occurrence of SCA6 in 6 out of 83 (13.33%) consecutive patients in a study based in eastern India, which was not observed before in the country. The apparent difference from the earlier studies could be due to the limited number of families assessed in each, while this is the largest number of patients studied in Kolkata. A clustering effect could also have been present in the previous studies.

The clinical features of patients of SCA6 in our study were more or less similar to what has been reported in the literature. However, in our study the mean disease duration of the disease was 3.67 years, whereas in the study of Jiang *et al*.,[23] it was 9.4 ± 4.3 years and that in the series of Schöls *et al*. it was 11 years. In our study we found cerebellar atrophy in MRI in 4 (66.67%) of the 6 patients, and sensory axonal neuropathy in the form of reduced sensory nerve action potential in 2 (33.33%) subjects.

It is of some interest that SCA2 outnumbered the other varieties in this part of the country when the issue of ethnicity was not considered, whereas SCA3 turned out to be the commonest variety among ethnic Bengalis in other studies.[11-13] No sign could be found as exclusive to SCA6, though cerebellar signs such as dysdiadochokinesia, dysmetria, and impaired heel-shin test were observed in all the cases, and nystagmus and dysmetria in more than 80% of the cases. The higher incidence of SCA6, as observed in the present study, could be due to the fact that the previous studies did not have the provision to use the specific primer for SCA6 or, alternatively and remotely, it could be due to new mutations.

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Conflicts of interest
There are no conflicts of interest.

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