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Clinical Study

# Profile of extrapyramidal manifestations in 85 patients with spinocerebellar ataxia type 1, 2 and 3

Ketan Jhunjhunwala [a], M. Netravathi [a], Meera Purushottam [b], Sanjeev Jain [b], Pramod Kumar Pal [a,*]

[a] Department of Neurology, National Institute of Mental Health & Neurosciences, Hosur Road, Bangalore 560029, Karnataka, India
[b] Department of Psychiatry, National Institute of Mental Health & Neurosciences, Bangalore, Karnataka, India

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ABSTRACT

This study aimed to determine the prevalence and type of extrapyramidal signs (EPS) in spinocerebellar ataxia (SCA) type 1, 2 and 3. Eighty-five patients with genetically confirmed SCA (SCA1 = 40, SCA2 = 28, SCA3 = 17) were evaluated for the prevalence and types of EPS. Forty-one SCA patients (48.2%) had one or more types of EPS. The prevalence of EPS was 60.7% in SCA2, 52.9% in SCA3, and 37.5% in SCA1. Among SCA2 patients, bradykinesia was the most frequent (35.3%), followed by reduced facial expression, postural tremor and dystonia (29.4% each), rest tremor, titubation and rigidity (23.5% each), and lip/jaw tremor and chorea (11.8% each). In SCA3 the common EPS were bradykinesia (44.4%), staring look, postural tremor and dystonia (33.3% each), and reduced facial expression and rigidity (22.2% each). In SCA1, staring look was the most common (53.3%), followed by dystonia and bradykinesia (33.3% each), and postural tremor (26.7%). In all three groups, there was no significant difference in the mean length of repeat of the abnormal allele between those with and without EPS. To conclude bradykinesia, staring look, dystonia and postural tremor were the most frequent EPS observed in SCA. In SCA1, these signs were seen more often in younger patients with early onset of symptoms.

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## 1. Introduction

The spinocerebellar ataxias (SCA) are a heterogeneous group of inherited disorders characterized by progressive ataxia. They were previously known as autosomal dominant cerebellar ataxias. Currently, SCA consist of 36 genetically distinct progressive neurodegenerative disorders [1]. The more prevalent types of SCA – SCA1, SCA2, SCA3 and SCA6 – are caused by expansion of a CAG repeat that encodes a polyglutamine tract in the affected protein [2]. SCA type 1, 2 and 3 are late onset autosomal dominant neurodegenerative disorders characterized by cerebellar ataxia associated with variable degrees of oculomotor abnormalities, pyramidal and extrapyramidal features, peripheral neuropathy, and cognitive impairment.

Various types of hypokinetic and hyperkinetic movement disorders are reported among SCA. In fact, movement disorders appear to be very common in SCA. Except for tics, all types of movement disorders can been observed in many types of SCA [3]. A variety of extrapyramidal signs (EPS) have been reported in SCA2 and SCA3, but less often in SCA1 [4]. In some patients, a non-ataxia manifestation may be the dominant or presenting feature, which at times presents a diagnostic challenge. Some movement disorders are more often seen in a specific subtype of SCA, and this knowledge may help in prioritizing genetic analysis for the patient [3]. Parkinsonian features are more common in SCA2 [5] and a Huntington's chorea-like presentation is more common in SCA17 [6]. When cerebellar ataxia is mild or even absent, SCA may not at first glance be suspected as a possible cause. Cerebellar atrophy on brain imaging or a family history suggesting dominant disease are useful clues in clinical practice to raise suspicion of SCA.

In a patient with an isolated movement disorder without cerebellar ataxia, genetic mutation testing should be carefully selected due to the low yield of these tests, with the two exceptions of SCA2 and SCA17 [3]. SCA17 is caused by the expansion above 44 units of a CAG/CAA repeat in the coding region of the TATA box binding protein (TBP) gene leading to an abnormal expansion of a polyglutamine stretch in the corresponding protein. SCA2 is a CAG repeat disorder leading to abnormal expression of the ATXN 2 gene resulting in abnormal ataxin 2 protein.

There are sparse data on EPS in large cohorts of SCA patients from a single ethnic group in the literature. It is also not clear if EPS correlate with age at symptom onset or the size of repeat lengths of the abnormal allele. The aims of our study were to (i) determine the prevalence and type of EPS in SCA type 1, 2 and 3, (ii) compare the findings between the patients with SCA1, SCA2,

* Corresponding author. Tel.: +91 80 2699 5147; fax: +91 80 2656 4830.
*E-mail address:* pal.pramod@rediffmail.com (P.K. Pal).

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and SCA3, and (iii) determine whether the length of the CAG repeat, age at disease onset or disease duration correlate with EPS in a specific SCA.

## 2. Subjects and methods

### 2.1. Patients

This study was conducted in the Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. It was approved by the Institute's Ethics Committee, NIMHANS. The nature and design of the study was explained to patients and informed consent was obtained.

All patients who had signs of cerebellar dysfunction with or without a positive family history were first clinically evaluated by a movement disorder specialist and then genetic testing was carried out to characterize the type of SCA. After informed consent was given, DNA was extracted from samples of peripheral blood leukocytes. All patients were genetically tested for the trinucleotide repeat expansions causing SCA1, SCA2 and SCA3 using a previously reported method [7].

### 2.2. Clinical evaluation

A detailed clinical evaluation was performed in each patient prior to genetic testing. Emphasis was given to the accurate and detailed documentation of EPS in addition to cerebellar and other neurological signs. The severity of ataxia was assessed in the majority of patients using the International Cooperative Ataxia Rating Scale (ICARS). The following EPS were specifically examined: rigidity, bradykinesia, reduced facial expression, staring look (bulging eyes), rest and action tremor, head, lip and jaw tremor (in addition to intention tremor of cerebellar dysfunction), myoclonic jerks, dystonia, athetosis and chorea.

Eighty-five patients who were found to be positive for SCA1, 2 and 3 were taken for analysis in the current study (SCA1 = 40, SCA2 = 28, SCA3 = 17). The prevalence and characterization of EPS and a comparison of those with and without EPS were done for each type of SCA.

### 2.3. Statistical analysis

The demographics and clinical characteristics of the patients with and without EPS were compared using unpaired *t*-tests. Comparative analysis of the prevalence of different types of EPS among the three subgroups of SCA was performed using the chi-squared test and Fisher's exact test. Results are reported as mean ± standard deviation.

## 3. Results

Men (76.5%) outnumbered women (23.5%) in our cohort of 85 patients with SCA. The mean age of the group was 35.6 ± 12.4 years, and the mean disease duration at the time of evaluation was 5.2 ± 4.5 years. The mean age, age at onset and disease duration in the three SCA groups were comparable (Table 1).

Forty-one patients (48.2%) had one or more types of EPS. EPS was present in 17 SCA2 patients (60.7%), nine SCA3 patients (52.9%) and 15 SCA1 patients (37.5%). In patients with EPS in SCA1, staring look was the most common (53.3%), followed by dystonia and bradykinesia (33.3% each), and postural tremor (26.7%). Among EPS in SCA2, bradykinesia was the most frequent (35.3%), followed by reduced facial expression, postural tremor and focal or segmental dystonia (29.4% each), rest tremor, titubation and rigidity (23.5% each), and lip/jaw tremor, chorea and jerks (11.8% each). In SCA3 the common EPS were bradykinesia (44.4%), staring look, postural tremor and dystonia (33.3% each), and reduced facial expression and rigidity (22.2% each) (Table 2).

**Table 1**
Demographics of patients with spinocerebellar ataxia type 1, 2 and 3

| | SCA (n = 85) | SCA1 (n = 40) | SCA2 (n = 28) | SCA3 (n = 17) |
|---|---|---|---|---|
| Women:Men | 20:65 | 10:30 | 5:23 | 5:12 |
| Age, years | 36.2 ± 12.5 | 35.3 ± 12.1 | 34.1 ± 14.1 | 40.2 ± 8.8 |
| AAO, years | 31.1 ± 12.1 | 30.4 ± 10.3 | 28.5 ± 14.1 | 36.2 ± 10.9 |
| Duration | 5.2 ± 4.5 | 5.1 ± 5.0 | 5.7 ± 4.4 | 4.4 ± 3.1 |

Data are presented as mean ± standard deviation.
AAO = age at onset of symptoms, SCA = spinocerebellar ataxia.

### 3.1. Prevalence of different types of EPS in SCA1, 2 and 3

#### 3.1.1. Dystonia

Thirteen of the 85 patients (15.2%) had evidence of dystonia, which was seen more often in SCA2 (17.9%) and SCA3 (17.6%) than in SCA1 (12.5%), though the difference was not statistically significant. Types of dystonia included five patients with generalized dystonia (SCA1 = 1, SCA2 = 1, SCA3 = 3), three patients with dystonia of the neck (one each in each SCA), three patients with facial dystonia in the form of grimacing (SCA1 = 2, SCA2 = 1), and one patient of SCA2 with lingual and foot dystonia. Using Fisher's exact test, there was no significant difference between SCA type 1, 2 and 3 for the presence of focal dystonia.

#### 3.1.2. Rigidity

Only six patients (7.1%) had rigidity of their limbs. Rigidity was found in four (14.3%) SCA2 patients and in two (11.3%) SCA3 patients, but no rigidity was seen in the SCA1 group ($p = 0.01$ for SCA2 *versus* SCA1, and $p = 0.03$ for SCA3 *versus* SCA1).

#### 3.1.3. Bradykinesia

Fifteen patients (17.6%) had appendicular and generalized bradykinesia. The sign was most often seen in SCA3 (n = 4, 23.5%) and SCA2 (n = 6, 21.4%) patients and was less common in SCA1 (n = 5, 12.5%). The differences were not statistically significant.

#### 3.1.4. Tremor

Rest tremor was uncommon in SCA (4.7%) and all four patients with rest tremor belonged to the SCA2 group (14.3%; $p = 0.01$ for SCA2 *versus* SCA1). Postural tremor was present in 13 patients

**Table 2**
Extrapyramidal signs in patients with spinocerebellar ataxia type 1, 2 and 3

| | SCA (n = 85) | SCA1 (n = 40) | SCA2 (n = 28) | SCA3 (n = 17) |
|---|---|---|---|---|
| Any EPS | 41 (48.2) | 15 (37.5) | 17 (60.7) | 9 (52.9) |
| Dystonia | 13 (15.2) | 5 (12.5) | 5 (17.9) | 3 (17.6) |
| Rigidity[a] | 6 (7.1) | 0 (0) | 4 (14.3) | 2 (11.3) |
| Bradykinesia | 15 (17.6) | 5 (12.5) | 6 (21.4) | 4 (23.5) |
| Rest tremor[b] | 4 (4.7) | 0 (0) | 4 (14.3) | 0 (0) |
| PT | 13 (15.3) | 4 (10) | 6 (20.9) | 3 (17.6) |
| Lip tremor | 3 (3.5) | 0 (0) | 2 (7.1) | 1 (5.9) |
| Chorea | 2 (2.3) | 0 (0) | 2 (7.1) | 0 (0) |
| Titubation[b] | 4 (4.7) | 0 (0) | 4 (14.3) | 0 (0) |
| Head thrust | 1 (1.2) | 1 (2.5) | 0 (0) | 0 (0) |
| Staring look | 14 (16.5) | 8 (20) | 3 (10.7) | 3 (23.5) |
| Hypomimia[c] | 8 (9.4) | 1 (2.5) | 5 (17.9) | 2 (11.8) |

[a] SCA1 *versus* SCA2 ($p = 0.01$), SCA1 *versus* SCA3 ($p = 0.03$).
[b] SCA1 *versus* SCA2 ($p = 0.01$).
[c] SCA1 *versus* SCA2 ($p = 0.04$).
Data are presented as n (%).
EPS = extrapyramidal sign, PT = postural tremor, SCA = spinocerebellar ataxia.

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