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Postural Tremor and Ataxia Progression in Spinocerebellar Ataxias

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Abstract

Background: Postural tremor can sometimes occur in spinocerebellar ataxias (SCAs). However, the prevalence and clinical characteristics of postural tremor in SCAs are poorly understood, and whether SCA patients with postural tremor have different ataxia progression is not known.

Methods: We studied postural tremor in 315 patients with SCA1, 2, 3, and 6 recruited from the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA), which consists of 12 participating centers in the United States, and we evaluated ataxia progression in these patients from January 2010 to August 2012.

Results: Among 315 SCA patients, postural tremor was most common in SCA2 patients (SCA1, 5.8%; SCA2, 27.5%; SCA3, 12.4%; SCA6, 16.9%; p = 0.007). SCA3 patients with postural tremor had longer CAG repeat expansions than SCA3 patients without postural tremor (71.67 ± 3.12 vs. 70.42 ± 3.96, p = 0.003). Interestingly, SCA1 and SCA6 patients with postural tremor had a slower rate of ataxia progression (SCA1, ß = -0.91, p < 0.001; SCA6, ß = -1.26, p = 0.025), while SCA2 patients with postural tremor had a faster rate of ataxia progression (ß = 1.54, p = 0.034). We also found that the presence of postural tremor in SCA2 patients could be influenced by repeat expansions of ATXN1 (ß = -1.53, p = 0.037) and ATXN3 (ß = 0.57, p = 0.018), whereas postural tremor in SCA3 was associated with repeat lengths in TBP (ß = 0.63, p = 0.041) and PPP2R2B (ß = -0.40, p = 0.032).

Discussion: Postural tremor could be a clinical feature of SCAs, and the presence of postural tremor could be associated with different rates of ataxia progression. Genetic interactions between ataxia genes might influence the brain circuitry and thus affect the clinical presentation of postural tremor.

Keywords: Spinocerebellar ataxias, postural tremor, genetics, cerebellum, neurodegeneration

Introduction

Spinocerebellar ataxias (SCAs) are autosomal dominant neurodegenerative disorders involving the cerebellum and related brain structures. While gait disturbance is the predominant feature of SCAs, SCA patients often have loss of hand dexterity and coordination. One such functional impairment is intention tremor, which can be a disabling symptom for many ataxic patients. The finger–nose–finger test is part of routine neurological examinations for cerebellar ataxia, which can be used to detect intention tremor.

Postural tremor is another form of action tremor. The prototypical neurological disorder of postural tremor is essential tremor (ET), and pathological alterations in the cerebellum have been identified in ET. Postural tremor can be a feature of Holmes tremor resulting from cerebellar damages as first described by Gordon Holmes. These findings suggest that the cerebellum might be important for postural tremor generation. Therefore, SCA patients with the degenerative cerebellum caused by repeat expansion-related protein aggregates might develop postural tremor.

Among hereditary ataxic disorders, patients with SCA10 or fragile X-associated tremor/ataxia syndrome have prominent postural tremor as the disease hallmark. Postural tremor has been reported to be present in other forms of SCA patients in several case reports, and can also be a prominent feature in CAG-repeat SCAs especially in SCA2. However, the sample size in these studies is moderate (n = 22–85), and there is no systemic comparison between SCA patients with and without postural tremor in terms of genetics and rate of clinical progression.

In the present study, we investigated the prevalence of postural tremor in SCAs in the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) cohort in North America. We also studied whether the presence of postural tremor would influence ataxia progression. Finally, we addressed whether other repeat expansion genes can be genetic modifiers for postural tremor in SCAs.

Methods

Study subjects

A total of 315 SCA patients (SCA1, 52; SCA2, 69; SCA3, 129; SCA6, 65) were longitudinally followed every 6 months for 2 years from January 2010 to August 2012 in the 12 medical centers of the CRC-SCA. All the participants signed consent forms approved by their respective local institutional review boards. The inclusion criteria were 1) definite genetic diagnosis of SCA1, 2, 3, or 6, either for the subject or for an affected family member with ataxia, 2) willingness of participation, and 3) age of 6 years and older. The exclusion criteria were 1) known recessive, X-linked, and mitochondrial ataxias, 2) exclusion of SCA1, 2, 3, and 6 by genetic tests, and 3) concomitant disorders that affect ataxia measurement used in this study.

All participants received a detailed clinical interview and neurological examination at baseline, which assessed the presence or absence of postural tremor by ataxia experts at their respective institutions. All ataxia specialists were well-trained neurologists and experts in the field of ataxia and movement disorders. Postural tremor was assessed by ataxia specialists based on the related maneuver from the Fahn–Tolosa–Marin tremor rating scale. During the neurological examination, postural tremor was assessed in two maneuvers: forward horizontal reach posture and lateral “wing beating” posture. Both the forward horizontal posture and the wing beating posture were held for 10 seconds, respectively. The tremors in both arms were assessed simultaneously. The presence of postural tremor was defined as the tremor observed during these maneuvers. The severity of ataxia was measured by the Scale for Assessment and Rating of Ataxia (SARA), which constitutes eight different domains of ataxia symptoms. SARA, an ataxia rating scale that has been used extensively in SCA research, is a continuous variable (0–40), with higher numbers corresponding with more severe ataxia. The presence of intention tremor was captured by the SARA subscale for the finger–nose–finger test.

Genetic analyses

All CAG repeat numbers of the respective SCA gene were determined using multiplex polymerase chain reaction, followed by capillary electrophoresis with internal standards in Dr. Stefan Pulst’s laboratory. Ten percent of DNA samples were verified using Sanger sequencing. Additionally, we determined the repeat expansions in ATXN1, ATXN2, ATXN3, ATXN4A, ATXN7, ATXN10, PPP2R2B, TRP, and FXN, for which the pathological repeat expansions cause SCA1, SCA2, SCA3, SCA6, SCA7, SCA10, SCA12, SCA17, and Friedreich’s ataxia, respectively.

Statistical analyses

We assessed the basic demographics of SCA patients with and without postural tremor. Chi-square and the Fisher exact test were used to compare non-continuous variables, testing for normality using the Kolmogorov–Smirnov test. For normally distributed variables, we used the Student t-test to compare postural tremor groups with non-postural tremor groups. For non-normally distributed variables, we used the Mann–Whitney U-test to compare postural tremor groups and non-postural tremor groups. A Bonferroni correction was made to adjust for multiple comparisons; therefore, p < 0.01 was considered significant in analyses of baseline features between SCA patients with and without postural tremor (five tests in each SCA).

We treated SCA1, 2, 3, and 6 groups as four independent cohorts. To study the average rates of disease progression in the SCA groups with and without postural tremor, we used repeated-measures linear regression (an exchangeable working within-subject correlation model by a generalized estimating equation (GEE)). In these models, we used SARA as the outcome variable, and the presence or absence of postural tremor at the baseline visit was treated as a dichotomous variable. We adjusted for age, gender, and CAG repeat expansions in these models. The ataxia progression of the two groups (postural tremor vs. non-postural tremor) during the 2-year follow up was measured by entering the interaction terms (postural tremor X time) into the GEE models. Coefficients of the interaction terms showed the differences of the rate of ataxia progression in two groups.
Postural Tremor and Ataxia Progression


In SCA1 and SCA6 patients, the presence of postural tremor predicted progression across all SCAs in these models, the presence of postural repeat expansions had a strong influence on the rate of ataxia into account age, gender, and CAG repeat expansions. While CAG different ataxia progression than those without postural tremor, the longer repeat alleles for the genetic modifier analysis.

This approach has been applied extensively to study the progression of SCAs. For the genetic modifier analyses, we constructed logistic regression models. We used the presence or absence of postural tremor as the outcome variable and the above-mentioned repeat expansion genes as the predictive variables, after adjusting for age and gender. Since most of the genes can cause dominant ataxia (except for FXY), we chose the longer repeat alleles for the genetic modifier analysis.

All statistical analyses were performed using SPSS software (version 23).

Results

Among 315 SCA patients, we found that SCA2 patients most commonly had postural tremor (27.5%), followed by SCA6 (16.9%) and SCA3 (12.4%). Postural tremor was rarely observed in SCA1 patients (5.8%) (Table 1). On the other hand, intention tremor was present in the majority of SCA patients (78.9%, 97.2%, 79.9%, and 84.5% in SCA1, 2, 3, and 6, respectively). Nearly all SCA patients with postural tremor also presented with intention tremor, except that one SCA3 patient with postural tremor did not have intention tremor (Supplemental Table 1).

We compared the basic demographics between SCA patients with and without postural tremor. SCA3 patients with postural tremor had higher CAG repeat expansion numbers than SCA3 patients without postural tremor (73.7 ± 3.1 vs. 70.4 ± 4.0, p = 0.003). CAG repeat expansion length did not differ in SCA1, 2, 6 patients with and without postural tremor. Moreover, there were no differences in age of onset, gender, disease duration, and baseline SARA scores between SCA1, 2, 3, and 6 patients with and without postural tremor (Table 2).

Next, we studied whether SCA patients with postural tremor had different ataxia progression than those without postural tremor, taking into account age, gender, and CAG repeat expansions. While CAG repeat expansions had a strong influence on the rate of ataxia progression across all SCAs in these models, the presence of postural tremor had diverse effects on ataxia progression in different SCAs. In SCA1 and SCA6 patients, the presence of postural tremor predicted slower ataxia progression (SCA1 β = −0.91, p < 0.001; SCA6 β = −1.28, p < 0.025). On the other hand, SCA2 patients with postural tremor had faster ataxia progression (β = 1.54, p < 0.034). Finally, the presence of postural tremor did not affect ataxia progression in SCA3 patients (Table 3).

In addition, we studied whether other ataxia-related repeat expansion genes could influence the clinical presentations of postural tremor in SCAs. We found that longer repeat alleles of the ATXN1 and ATXN3 genes were associated with a lower and higher likelihood, respectively, of postural tremor in SCA2 patients (ATXN1 β = −1.53, p = 0.037; ATXN3 β = 0.57, p = 0.018). In SCA3 patients, longer repeat alleles in TBP were associated with a higher likelihood of postural tremor, while longer repeat alleles in PPP2R2B were associated with a lower likelihood of postural tremor (TBP β = 0.63, p = 0.041; PPP2R2B β = −0.40, p = 0.032). The repeat expansions in other ataxic genes did not play significant roles in postural tremor in SCA1 and SCA6 patients in our models (Table 4).

Discussion

In the current study, we found that among SCAs, SCA2 patients most commonly have postural tremor. We also observed that the presence of postural tremor might predict ataxia progression in different SCAs. Finally, the disease-causing gene itself, as observed in SCA3, and the interactions between different ataxic genes, as seen in SCA2 and SCA3, can play important roles in the clinical features of SCAs.

The underlying brain circuitry of postural tremor in SCAs is not completely understood. The majority of SCA patients have intention tremor, while only a small subset of SCA patients have postural tremor, suggesting different brain circuitries involved in these two forms of action tremor. The prototypical disorder of postural tremor is ET, which shares some pathological features with SCAs in terms of cerebellar degeneration. Loss of Purkinje cell (PC) and PC axonal torpedoes has been observed both in ET and SCA cases, although ET cases have a much milder degree of pathological alterations than SCA cases. Olivocerebellar involvement has long been postulated to be involved in postural tremor in ET. Olivary neurons send their axons into the cerebellar cortex to form climbing fibers (CFs) that innervate PCs, and overactivation of CFs by a compound called harmaline could induce ET-like tremor in rodents. Interestingly, both ET and SCA cases have morphological alterations in CFs. Specifically, both ET and SCA cases have decreased CF synaptic density. However, ET cases have CFs extending into the parallel fiber synaptic territory on PC dendrites, whereas SCA cases have regressed CFs. It is possible that differential involvement of PCs.
Table 2. Baseline Features of 315 Participants Grouped by Neurological Features in the Different Subtypes of SCA

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Postural Tremor</th>
<th>No Postural Tremor</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1, n = 5</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>SCA2, n = 129</td>
<td>3</td>
<td>126</td>
<td>0.007</td>
</tr>
<tr>
<td>SCA3, n = 65</td>
<td>65</td>
<td>113</td>
<td>0.051</td>
</tr>
<tr>
<td>SCA4, n = 65</td>
<td>65</td>
<td>113</td>
<td>0.052</td>
</tr>
<tr>
<td>SCA5, n = 32</td>
<td>23</td>
<td>9</td>
<td>0.007</td>
</tr>
<tr>
<td>SCA6, n = 69</td>
<td>19</td>
<td>50</td>
<td>0.013</td>
</tr>
</tbody>
</table>

| Age of onset (years) | Median | 25.00 | 41.18 | 0.001 |
| Gender, M : W | 25 : 24 | 15 : 6  | 0.292  |
| CAG repeat (numbers) | Median | 50.00 | 45.83 | 0.118 |
| Disease duration (years) | Median | 5.33 | 10.43 | 0.234 |
| Baseline SARA score | Median | 16.42 | 19.34 | 0.663 |

Values represent mean ± standard deviation or number, and for variables with non-normal distribution, the median is reported as well. The value in bold represents statistical significance.

1 Two independent samples t-test.
2 Chi-square test.
3 Two independent samples Mann–Whitney U test.

We did not capture the severity of postural tremor, which could be the effects of which we did not analyze in detail. Nonetheless, we medicating can be confounding factors and may be tremorigenic, assessment; nonetheless, the raters are all experts specialized in ataxia obtain inter-rater reliability or formal rater training for tremor should be taken into account in future studies. Third, we did not tremor, which can change during the disease progression. This issue required. Second, only a baseline measurement was made of postural tremor. Nonetheless, a sample size of 49 in each group is able to detect the difference in the prevalence of postural tremor in our current study between SCA2 (27.5%) and SCA1 (5.8%), at the significance level of 0.05 and with 80% power. Although all four types of SCAs in our study had a sample size above this threshold, our sample size is not sufficient to detect more subtle differences. Therefore, the current study should be considered exploratory, and a future study with a larger sample size and a longer follow-up is required. Second, only a baseline measurement was made of postural tremor, which can change during the disease progression. This issue should be taken into account in future studies. Third, we did not obtain inter-rater reliability or formal rater training for tremor assessment; nonetheless, the raters are all experts specialized in ataxia and movement disorders. Moreover, the prevalence of postural tremor in SCAs in the current study is similar to a previous study. Fourth, we did not capture the severity of postural tremor, which could be measured by the Glass Scale. Fifth, we did not perform neurophysiological studies to characterize postural tremor in each of the SCAs, which could provide further insight into the tremor mechanism by comparing postural tremor in SCAs with that in ET and/or enhanced physiological tremor. This would advance our understanding of whether postural tremor in SCAs is central neurogenic tremor or is related to abnormal mechanical reflex oscillations. Sixth, medications can be confounding factors and may be tremorigenic, the effects of which we did not analyze in detail. Nonetheless, we and CFs during the degenerative process of SCAs produces postural tremor. Thus, postural tremor could serve as an indicator of underlying pathology.

However, studies also showed that the inferior olive might not be involved in ET and postural tremor could be generated by gabaergic dysfunction of the cerebellar dentate nucleus and thalamus within the cerebellothalamicortical circuit. Interestingly, the thalamus is preferentially affected in SCA2 patients, which could explain the higher occurrence of postural tremor in SCA2.

Although SCAs are monogenetic disorders with complete penetrance, we are just beginning to understand the genetic interactions between different repeat expanded genes in these ataxic disorders. Interestingly, proteins from the ataxia-causing genes could form complex interaction networks to govern proper cerebellar physiology and function. The interaction between ataxia genes has been found to influence the age of ataxia onset in SCA patients. Our study further highlights that this interaction between ataxia genes can additionally affect the clinical presentations in SCA patients.

Our study has several strengths. First, our study is based on the largest cohort of SCA patients in North America with a longitudinal follow-up. Therefore, we could adequately address whether SCA patients with postural tremor have a different clinical progression. Second, we comprehensively studied the genetic modifiers in a panel of repeat expansion genes, which allowed us to uncover the interactions between ataxia genes. However, our study also has several limitations. First, our sample size remained modest, making our study more prone to type 2 errors. In particular, we only had three SCA1 patients with postural tremor. Nonetheless, a sample size of 49 in each group is able to detect the difference in the prevalence of postural tremor in our current study between SCA2 (27.5%) and SCA1 (5.8%), at the significance level of 0.05 and with 80% power. Although all four types of SCAs in our study had a sample size above this threshold, our sample size is not sufficient to detect more subtle differences. Therefore, the current study should be considered exploratory, and a future study with a larger sample size and a longer follow-up is required. Second, only a baseline measurement was made of postural tremor, which can change during the disease progression. This issue should be taken into account in future studies. Third, we did not obtain inter-rater reliability or formal rater training for tremor assessment; nonetheless, the raters are all experts specialized in ataxia and movement disorders. Moreover, the prevalence of postural tremor in SCAs in the current study is similar to a previous study. Fourth, we did not capture the severity of postural tremor, which could be measured by the Glass Scale. Fifth, we did not perform neurophysiological studies to characterize postural tremor in each of the SCAs, which could provide further insight into the tremor mechanism by comparing postural tremor in SCAs with that in ET and/or enhanced physiological tremor. This would advance our understanding of whether postural tremor in SCAs is central neurogenic tremor or is related to abnormal mechanical reflex oscillations. Sixth, medications can be confounding factors and may be tremorigenic, the effects of which we did not analyze in detail. Nonetheless, we and CFs during the degenerative process of SCAs produces postural tremor. Thus, postural tremor could serve as an indicator of underlying pathology.
previously reviewed medication use in this SCA cohort and found that five medications were most commonly used (coq10, statins, vitamin E, riluzole, and varenicline), none of which is associated with tremor. 

Seventh, we did not record tremor in the head, voice, or face. However, these types of tremor were uncommon among SCAs, except for ataxia with vitamin E deficiency, which is often associated with head tremor. Finally, we only focused on the repeat expansion in selected ataxia genes in the genetic modifier analyses. Variants in other ataxia genes, along with expansions of the FMR1 gene, might also play a role, which requires further exploration.

Table 3. Longitudinal SARA Scores of the Different Neurological Symptoms in the GEE Model

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression Coefficients of SARA Score¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCA1</td>
</tr>
<tr>
<td>Age of first visit (years)</td>
<td>0.62 (0.001)</td>
</tr>
<tr>
<td>Gender²</td>
<td>4.61 (0.013)</td>
</tr>
<tr>
<td>CAG repeat (numbers)</td>
<td>1.57 (0.001)</td>
</tr>
<tr>
<td>Postural tremor³</td>
<td>-3.66</td>
</tr>
<tr>
<td>Visit time</td>
<td>1.01 (0.001)</td>
</tr>
<tr>
<td>Postural tremor × visit time</td>
<td>-0.91 (0.001)</td>
</tr>
</tbody>
</table>

Abbreviations: SARA = Scale for Assessment and Rating of Ataxia; GEE = Generalized Estimating Equation; SCA = Spinocerebellar Ataxia. ¹All regression coefficients and p-values were calculated in the GEE model, adjusting for age of first visit, gender, CAG repeat, neurological symptom, and neurological symptom × visit time. ²Men = 0, Women = 1. ³No postural tremor = 0; postural tremor = 1.

Table 4. Logistic Regression Analyses for Influencing Factors of Postural Tremor in the Different Subtypes of SCA

<table>
<thead>
<tr>
<th>Variables</th>
<th>Dependent Variable: Postural Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCA1</td>
</tr>
<tr>
<td></td>
<td>β     OR  p</td>
</tr>
<tr>
<td>Age of first visit (years)</td>
<td>-1.51 0.22 0.999</td>
</tr>
<tr>
<td>Gender¹</td>
<td>-28.29 0.00 0.999</td>
</tr>
<tr>
<td>ATXN1 (SCA1) repeat numbers</td>
<td>-0.54 0.58 1.000</td>
</tr>
<tr>
<td>ATXN2 (SCA2) repeat numbers</td>
<td>-13.02 0.00 0.999</td>
</tr>
<tr>
<td>ATXN3 (SCA3) repeat numbers</td>
<td>-0.26 0.78 1.000</td>
</tr>
<tr>
<td>CAGA4A1A (SCA6) repeat numbers</td>
<td>3.59 0.07 0.001</td>
</tr>
<tr>
<td>ATXN7 (SCA7) repeat numbers</td>
<td>-0.06 0.94 1.000</td>
</tr>
<tr>
<td>ATXN19 (SCA10) repeat numbers</td>
<td>-1.71 0.18 1.000</td>
</tr>
<tr>
<td>PPP2R2B (SCA12) repeat numbers</td>
<td>-9.07 0.00 0.998</td>
</tr>
<tr>
<td>TBP (SCA17) repeat numbers</td>
<td>-14.51 0.00 0.999</td>
</tr>
<tr>
<td>FXV (FA) repeat numbers</td>
<td>0.26 1.29 1.000</td>
</tr>
</tbody>
</table>

The values in bold represent statistical significance. ¹Men = 0, Women = 1.
In conclusion, our study indicates that postural tremor could be present in the four most common SCAs and that SCA patients with postural tremor might have a different rate of ataxia progression. Genetic interactions between ataxia genes might influence the brain circuitry involved and thus affect the clinical presentation of postural tremor.

References


3. Schmitz-Hubsc...


