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Tremor in the Degenerative Cerebellum: Towards the Understanding of Brain Circuitry for Tremor

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Abstract

Background: Cerebellar degenerative pathology has been identified in tremor patients; however, how the degenerative pathology could contribute to tremor remains unclear. If the cerebellar degenerative pathology can directly drive tremor, one would hypothesize that tremor is likely to occur in the diseases of cerebellar ataxia and follows the disease progression in such disorders.

Methods: To further test this hypothesis, we studied the occurrence of tremor in different disease stages of classical cerebellar degenerative disorders: spinocerebellar ataxias (SCAs). We further separately analyzed postural tremor and rest tremor, two forms of tremor that both involve the cerebellum. We also explored tremor in different subtypes of SCAs.

Results: We found that 18.1% of SCA patients have tremor. Interestingly, SCA patients with tremor have worse ataxia than those without tremor. When stratifying patients into mild, moderate, and severe disease stages according to the severity of ataxia, moderate and severe SCA patients more commonly have tremor than those with mild ataxia, the effect most prominently observed in postural tremor of SCA3 and SCA6 patients. Finally, tremor can independently contribute to worse functional status in SCA2 patients, even after adjusting for ataxia severity.

Conclusions: Tremor is more likely to occur in the severe stage of cerebellar degeneration when compared to mild stages. Our results partially support the cerebellar degenerative model of tremor.

Keywords

tremor; cerebellum; neurodegeneration

Introduction

Tremor is the most common movement disorder phenomenology [1]; however, how tremor could be generated from the abnormal brain circuitry remains poorly understood, which is a major hurdle for developing effective therapy. Among tremor disorders, essential tremor (ET) is the most common, and many neuroimaging and clinical studies of ET point towards the cerebellum as the key brain region involved in tremor [2–6]. Therefore, these is an extensive search for brain structural changes within the cerebellum which might relate to tremor generation. As a result, several pathological features have been identified in the ET cerebellum, including Purkinje cell (PC) loss [7,8], PC axonal torpedoes [9,10], and heterotopic PCs [11], which can also be observed in cerebellar degenerative disorders such as spinocerebellar ataxia type 1 (SCA1) or multiple system atrophy [12]. These observations raise the question whether ET is a degenerative disorder. Furthermore, whether degeneration

of the cerebellum could cause both ataxia and tremor along a spectrum of cerebellar dysfunction still remains unknown.

Spinocerebellar ataxias (SCAs) are a group of genetic disorders that cause cerebellar ataxia [13]. Pathology of SCAs shows extensive PC loss and other associated cerebellar degeneration [14–17]. The most common SCAs are those with pathological CAG repeat expansions, including SCA1, 2, 3, and 6, with defined age of onset that is inversely correlated with the length of the CAG repeat [18]. In addition, the natural history of these SCAs is well-studied, allowing us to track the disease progression and to study the clinical features in different disease stages. Based on these unique features and past studies on SCAs, we choose to use SCAs as model systems of classical cerebellar degenerative disorders to test the hypothesis that cerebellar degeneration can cause tremor. We previously found that a subset of ataxia patients have tremor from the natural history study of SCAs [19]; however, the association between cerebellar degeneration and tremor remains unclear. In order to study the relationship between tremor and cerebellar degeneration, we used the severity of ataxia as an approximation for the degree of cerebellar degeneration. If tremor could generate from the degenerative cerebellum, we would expect tremor to occur more often in SCAs with severe ataxia as compared to those with mild ataxia. The knowledge gained will help us to broadly advance our understanding of the cerebellar degeneration in ataxia and tremor.

Methods

Study Subjects

The study participants were genetically-confirmed SCA patients, evaluated by ataxia specialists during January 2010 to August 2012 in the 12 medical centers of the Clinical Research Consortium for SCAs (CRC-SCA). The uniform study protocol was approved by the respective local institutional review boards, and all participants signed the consent forms. Our inclusion criteria were 1) the presence of ataxia, 2) definite genetic diagnosis of SCA1, 2, 3, or 6 by the determination of the pathological CAG repeat number, either for the subject or for another affected family member with ataxia, 3) willingness to participate in the study, and 4) age of 6 years or older. Our 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.

All participants were asked to provide blood samples for CAG repeat determination and associated repeats as previously described [19,20] and basic demographics were recorded. Clinical interviews and neurological examinations were performed face-to-face with each participant by ataxia specialists, who assessed the presence or absence of postural and rest tremor. Ataxia specialists assessed postural tremor using the related maneuver from the Fahn-Tolosa-Marin tremor rating scale [21]. Tremors in both arms were assessed simultaneously in the neurological examination using two maneuvers, lateral “wing beating” posture and forward horizontal reach posture. Rest tremor was observed in both arms at the rest position, as instructed in the Unified Parkinson’s Disease Rating Scale (UPDRS) [22]. As the majority of SCA patients have intention tremor [19], which could be part of the ataxia symptom and thus likely non-specific, we did not use intention tremor as part of the

tremor assessment. The severity of ataxia was measured by the Scale of Assessment and Rating of Ataxia (SARA, 0-40), which measured 8 domains of ataxia symptoms with the higher scores indicating more severe ataxia [23]. We measured the participants' functional status using the Unified Huntington's Disease Rating Scale part IV (UHDRS-IV) which ranges from 0 to 25, with higher scores indicating better functional status.

Genetic Analyses

DNA samples from blood of the participants were obtained and CAG repeat expansions in *ATXN1* (SCA1), *ATXN2* (SCA2), *ATXN3* (SCA3), *CACNA1A* (SCA6) were determined in Dr. Stefan Pulst's laboratory. Multiplex PCR was used, followed by capillary electrophoresis with internal standards. Re-genotyping and Sanger sequencing were performed to verify the CAG repeat length in 10% of all samples.

Statistical Analysis

We first compared the basic demographics and ataxia severity in SCA patients, regardless of the genotypes, with and without tremor (postural tremor, rest tremor, or both) as the primary analysis since both postural and rest tremor are thought to involve the cerebellum [7,8,24,25]. We excluded subjects with missing information on postural or rest tremor (4 SCA1, 4 SCA2, 9 SCA3, 4 SCA6) in the CRC-SCA cohort. We further stratified SCA patients into mild, moderate, and severe ataxia based on the SARA scores (mild: ≤ 10, moderate > 10 and < 20, severe ≥ 20) and studied the occurrence of tremor in these subgroups. We chose these cutoffs to define the severity of ataxia because these values are associated with the degree of gait dysfunction, which can indicate the milestones for ataxia progression (99.0% of mild ataxia patients can walk independently without support, 69.3% of moderate ataxia patients can at least walk with support of one stick, whereas 90.8% of severe ataxia patients need at least a stroller to walk or are wheelchair-dependent in CRC-SCA cohort).

We further divided SCA patients based on their genotypes (SCA1, 2, 3, or 6) or based on the tremor characteristics (postural tremor or rest tremor) to study in detail the interactions of SCA subtypes and tremor.

All statistical analyses were performed using SPSS software (version 24). For continuous variables, we first tested the normality of the variables using the Kolmogorov-Smirnov test. For normally distributed variables, we compared between two groups using Student t-test. For non-normally distributed variables, we used Mann-Whitney U-test. Chi-square tests were used for non-continuous variables. All tests were conducted at the two-tailed α-level of 0.05.

Results

Among the 315 SCA patients in the CRC-SCA cohort, tremor could be observed in 18.1% of patients. SCA patients with and without tremor did not differ in age of ataxia onset, gender, or age of the assessment (Table 1). Interestingly, SCA patients with tremor have a significantly higher SARA scores than those without tremor (18.61 ± 6.81 vs. 14.32 ± 8.21, $p < 0.001$). We further explored the relationship between the severity of ataxia and tremor by

dividing SCA patients into mild, moderate, and severe ataxia. We found that only 5.9% of SCA patients in the mild disease stage have tremor, whereas 21.3% and 27.6% of moderate and severe SCA patients, respectively, have tremor ($p < 0.001$), suggesting that tremor can occur more frequently in moderate and severe stages of the diseases (Table 1).

We next investigated the SCA subtypes and tremor. Tremor occurs most commonly in SCA2 (30.9%), followed by SCA6 (22.4%) and SC A3 (14.3%). SCA1 patients have the least tremor (5.6%). We found that SCA2, 3, and 6 patients with tremor had on average 4-point higher SARA scores than those without tremor (SCA2: 19.92 ± 7.65 vs. 15.48 ± 6.51, $p = 0.027$, SCA3: 18.42 ± 6.85 vs. 14.54 ± 9.00, $p = 0.036$, SCA6: 17.38 ± 4.47 vs. 13.59 ± 8.05, $p = 0.023$) while SCA1 patients also have a similar trend but did not reach statistical significance (16.83 ± 11.86 vs. 13.52 ± 8.11, $p = 0.678$) (Table 2). When stratifying patients into mild, moderate, and severe disease stages, tremor occurs more commonly in moderate and severe disease stages in SCA3 ($p = 0.032$) and SCA6 ($p = 0.014$) whereas there are no significant differences in SCA1 ($p = 0.891$) and SCA2 ($p = 0.076$) subgroups (Table 2).

We further compared the interactions of tremor subtypes and SCA genotypes. Since tremor occurs in a similar degree in moderate and severe ataxic patients (Table 1), we grouped moderate and severe ataxic patients in this analysis. We found that postural tremor occurs more often in moderate and severe SCA3 and SCA6 patients compared to those with mild ataxias (SCA3: 15.6% vs. 4.1%, $p = 0.045$, SCA6: 27.7% vs. 0.0%, $p = 0.009$). Postural tremor occurs in a similar degree in moderate and severe vs. mild SCA1 and SCA2 patients (SCA1: 3.1% vs. 4.5%, $p = 0.786$, SCA2: 27.6% vs. 30.0%, $p = 0.875$) (Table 3). None of the mild SCA patients have rest tremor. Even in severe ataxic patients, rest tremor only occurs in 3-5% of the patients except for SCA2 (15.5%) (Table 3).

We next asked whether postural and rest tremor frequently co-occur in SCAs. In SCA1, 3, and 6, no patient had both types of tremor, while the majority of SCA3 and SCA6 patients with tremor have postural tremor without rest tremor (Table 4). In SCA2, there are 10.3% of patients with both types of tremor, suggesting that postural tremor and rest tremor frequently co-occur in SCA2 (Table 4).

We further studied the relationship between tremor and dystonia, two clinical features associated with cerebellar dysfunction. We found that tremor and dystonia are only marginally associated in SCA3 but not associated in other types of SCAs (Supplementary table 1).

One of the relevant clinical questions is whether tremor can independently contribute to worse functional status in SCA patients, suggesting that both tremor and ataxia generated from cerebellar degeneration can be disabling. To address this, we constructed linear regression models to test the contribution of tremor and ataxia in SCAs to functional status measurement by UHDRS after adjusting for age, gender, and pathological CAG repeats. When all SCA subtypes were combined, tremor was associated with worse functional status ($\beta = -1.71$, $p = 0.003$) (Table 5). When the different SCA subtypes were analyzed separately, tremor was associated with worse functional status in SCA2 ($\beta = -3.83$, $p < 0.001$) while the other subtypes of SCAs showed the same trend without statistical

significance (SCA1 β = −2.82, $p = 0.186$; SCA3: β = −1.03, $p = 0.282$; SCA6: β = −0.93, $p = 0.464$) (Table 5).

Discussion

In the present study, we found that tremor occurs more frequently in the later stage of the cerebellar degeneration. Interestingly, the association between tremor and ataxia is not linear. While mild ataxia is associated with less tremor, moderate and severe ataxias are associated with a similar degree of tremor (Table 1), suggesting the dynamic regulations of cerebellar circuitry for tremor and ataxia during the degenerative process. The association of tremor and ataxia is most obvious in SCA3 and SCA6 patients. Postural tremor is the tremor subtype that is mostly associated with ataxia while the association of rest tremor and ataxia is less robust. In addition, we found that rest tremor and postural tremor might be independent to each other in the context of degenerative cerebellum, with the exception of SCA2, suggesting the different circuitries involved. Finally, we found that tremor could worsen the functional status of SCA patients, independent of ataxia. In summary, our research partly supports the cerebellar degenerative hypothesis of tremor. However, not all the SCA patients have tremor, raising the question that additional regulatory mechanisms exist, which requires further investigation.

ET is a classical tremor disorder and several pathological features of ET exhibit similarities to SCA patients, but to a milder degree, suggesting the common components of brain circuitry alterations between tremor and ataxia. For example, loss of PCs, increased number of PC axonal torpedoes, and decreased climbing fiber synaptic density have been observed in both SCA and ET patients [26,27]. However, different cerebellar pathology has also been identified in these two groups of patients. For instance, ET patients have extending climbing fibers to the outer portion of the molecular layer whereas SCA patients have prominent regression of climbing fibers [28]. Studying the similarities and differences between ET and SCA patients with and without tremor will further shed light in our future understanding of the cerebellar circuitries that produce ataxia and tremor.

There are limitations to this study. First, different SCAs may represent different types of cerebellar degeneration. For example, patients with SCA3 have relatively preserved PC counts whereas patients with SCA1, 2, and 6 have prominent PC loss [29]. Nonetheless, we observed the most prominent effects on the association between ataxia and tremor in SCA3 and SCA6, but not SCA1 and SCA2, which might suggest that other components such as compensatory changes within the cerebellar circuitry might be important for tremor generation. Second, the sample size remains moderate. A larger sample size with trans-continental collaboration is needed to further explore the heterogeneity of postural and rest tremor in SCA patients. Third, our study is not specifically designed to study tremor in SCAs; nonetheless, the majority of the ataxia specialists involved in the study have received movement disorders fellowship training. In addition, rest tremor measurement might not be accurate if the patients are not completely relaxed; therefore, our study includes the analysis to combine both rest and postural tremor, which provide information on overall tremor in cerebellar degeneration. Fourth, we did not use an objective measure to define the frequency of the rhythmicity of tremor, which might be distinct in different stages of subtypes of

SCAs. Fifth, we used the ataxia severity as an estimate for the degree of cerebellar degeneration. More detailed structural neuroimaging studies will yield a more accurate assessment of cerebellar degeneration and provide the region of the cerebellar atrophy associated with tremor. Sixth, many SCAs also have extra-cerebellar involvement, which can collectively contribute to tremor [30]. Finally, we did not have detailed characterization of tremor severity, which can be used in future studies to investigate whether tremor becomes more severe as ataxia progresses in SCA patients.

Our study can also help to advance the current knowledge of the interplay between tremor, dystonia, and ataxia, three symptoms associated with cerebellar dysfunction. Ataxia is a classical symptom of cerebellar disorders. Tremor and dystonia have recently been identified to have cerebellar involvement [31, 32]. Our ataxia cohort provide evidence that tremor, dystonia, and ataxia could co-occur during cerebellar degeneration. Similarly, genetically modified mice with cerebellar dysfunction can also have these three symptoms [33], highlighting the abnormal cerebellar circuitry in these movement disorders. How can dysfunctional cerebellum generate these symptoms? One explanation is that abnormal firing patterns of Purkinje cells can directly drive diverse movements, including tremor and/or dystonia [31]. Depending on the underlying disease processes affecting Purkinje cell firing, these three symptoms could co-occur or change over the course of disease. In addition, one of the most important functions of the cerebellum is motor timing; therefore, tremor and dystonia might be related to abnormal motor timing of the cerebellum [34–39]. In summary, our study provides a way to begin to understand the complex relationship between tremor, dystonia, and ataxia in humans, which will advance our knowledge in cerebellar motor control.

In conclusion, we found that both postural and rest tremor can occur in the degenerative cerebellum in patients with SCAs but in a subtype-specific manner. Our findings support the theory that the cerebellar degenerative process can contribute to tremor and clinicians should also pay attention to tremor symptoms in caring for ataxia patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline features of 315 participants grouped by neurological features

	Tremor	No tremor	p-value
n (%)	57 (18.1)	258 (81.9)	
Age (years)	54.95 ± 15.06 Median = 59.00	54.00 ± 13.32 Median = 54.00	0.486 [c]
Gender, M : W	32 : 25	136 : 122	0.639 [a]
Age of onset (years)	39.11 ± 13.45	41.91 ± 12.67	0.135 [b]
SARA score	18.61 ±6.81 Median = 18.50	14.32 ±8.21 Median = 13.00	**0.000** [c]
Ataxia severity (SARA)			**0.000** [a]
Mild (%)	6 (5.9)	95 (94.1)	
Moderate (%)	27 (21.3)	100 (78.7)	
Severe (%)	24 (27.6)	63 (72.4)	

Abbreviations: SCA = Spinocerebellar Ataxia; SARA = Scale for Assessment and Rating of Ataxia Values represent mean ± standard deviation or number, and for variables with non-normal distribution, the median is reported as well.

[a] Chi-square test

[b] 2 independent samples t-test

[c] 2 independent samples Mann-Whitney U test

Table 2.

Baseline features of 315 participants grouped by neurological features in the different subtypes of SCA

	SCA 1 *n* = 54		*p*-value	SCA 2 *n* = 68		*p*-value	SCA 3 *n* = 126		*p*-value	SCA 6 *n* = 67		*p*-value
	Tremor	**No tremor**		**Tremor**	**No tremor**		**Tremor**	**No tremor**		**Tremor**	**No tremor**	
n (%)	3 (5.6)	51 (94.4)		21 (30.9)	47 (69.1)		18 (14.3)	108 (85.7)		15 (22.4)	52 (77.6)	
Age (years)	49.33 ± 28.57 Median = 37.00	50.88 ± 11.83 Median = 52.00	0.590 [c]	51.10 ± 13.90	50.83 ± 13.01	0.941 [b]	51.56 ± 12.80 Median = 56.50	51.18 ± 12.25 Median = 50.00	0.853 [c]	65.53 ± 12.32	65.79 ± 10.56	0.943 [b]
Gender, M : W	3 : 0	25 : 26	0.086 [a]	15 : 6	24 : 23	0.117 [a]	9 : 9	55 : 53	0.942 [a]	5 : 10	32 : 20	0.053 [a]
CAG repeat (numbers)	50.00 ± 7.81 Median = 54.00	45.80 ± 4.08 Median = 46.00	0.271 [c]	40.52 ± 3.82 Median = 40.00	39.66 ± 2.80 Median = 39.00	0.220 [c]	72.00 ± 4.26 Median = 72.00	70.82 ± 4.16 Median = 71.00	0.198 [c]	22.60 ± 1.45 Median = 22.00	22.31 ± 0.73 Median = 22.00	0.827 [c]
Age of onset (years)	37.33 ± 15.37	40.67 ± 11.27	0.745 [b]	36.00 ± 14.18	36.83 ± 11.19	0.814 [b]	35.83 ± 11.70 Median = 38.50	39.34 ± 12.03 Median = 40.00	0.398 [c]	47.73 ± 11.28	53.08 ± 10.06	0.113 [b]
SARA score	16.83 ± 11.86	13.52 ± 8.11	0.678 [b]	19.92 ± 7.65	15.48 ± 6.51	**0.027** [b]	18.42 ± 6.85 Median = 18.75	14.54 ± 9.00 Median = 13.25	**0.036** [c]	17.38 ± 4.47	13.59 ± 8.05	**0.023** [b]
Ataxia severity			0.891 [a]			0.076 [a]			**0.032** [a]			**0.014** [a]
Mild (%)	1 (4.5)	21 (95.5)		3 (30.0)	7 (70.0)		2 (4.1)	47 (95.9)		0 (0.0)	20 (100.0)	
Moderate (%)	1 (5.0)	19 (95.0)		8 (21.1)	30 (78.9)		8 (20.0)	32 (80.0)		10 (34.5)	19 (65.5)	
Severe (%)	1 (8.3)	11 (91.7)		10 (50.0)	10 (50.0)		8 (21.6)	29 (78.4)		5 (27.8)	13 (72.2)	

Abbreviations: SCA = Spinocerebellar Ataxia; SARA = Scale for Assessment and Rating of Ataxia

Values represent mean ± standard deviation or number, and for variables with non-normal distribution, the median is reported as well.

[a] Chi-square test

[b] 2 independent samples t-test

[c] 2 independent samples Mann-Whitney U test

Table 3.

Tremor prevalence grouped by ataxia severity in different subtypes of SCA

	SCA1 *n* = 54			SCA2 *n* = 68			SCA3 *n* = 126			SCA6 *n* = 67		
	Mild	**Moderate or Severe**	**p** [a]	**Mild**	**Moderate or Severe**	**p** [a]	**Mild**	**Moderate or Severe**	**p** [a]	**Mild**	**Moderate or Severe**	**p** [a]
Postural tremor			0.786			0.875			**0.045**			**0.009**
Yes (%)	1 (4.5)	1 (3.1)		3 (30.0)	16 (27.6)		2 (4.1)	12 (15.6)		0 (0.0)	13 (27.7)	
No (%)	21 (95.5)	31 (96.9)		7 (70.0)	42 (72.4)		47 (95.9)	65 (84.4)		20 (100.0)	34 (72.3)	
Rest tremor			0.403			0.181			0.105			0.349
Yes (%)	0 (0.0)	1 (3.1)		0 (0.0)	9 (15.5)		0 (0.0)	4 (5.2)		0 (0.0)	2 (4.3)	
No (%)	22 (100.0)	31 (96.9)		10 (100.0)	49 (84.5)		49 (100.0)	73 (94.8)		20 (100.0)	45 (95.7)	

Abbreviations: SCA = Spinocerebellar ataxia

[a]Chi-square test

Table 4.

The presence of postural tremor and rest tremor in the different subtypes of SCA

		SCA1 *n* = 54			SCA2 *n* = 68			SCA3 *n* = 126			SCA6 *n* = 67		
		Postural tremor											
		Yes	No	p [a]	Yes	No	p [a]	Yes	No	p [a]	Yes	No	p [a]
Rest tremor	Yes	0 (0.0)	1 (1.9)	0.843	7 (10.3)	2 (2.9)	**0.000**	0 (0.0)	4 (3.2)	0.472	0 (0.0)	2 (3.0)	0.481
	No	2 (3.7)	51 (94.4)		12 (17.6)	47 (69.1)		14 (11.1)	108 (85.7)		13 (19.4)	52 (77.6)	

Abbreviations: SCA = Spinocerebellar ataxia

Values represent number (%)

[a]Chi-square test

Table 5.

Linear regression analyses for the influencing factors of UHDRS score

Variables	Regression coefficients of UHDRS score [a]				
	All SCAs	**SCA1**	**SCA2**	**SCA3**	**SCA6**
Age (years)	−0.03	−0.10	0.04	−0.07	−0.15**
Gender [b]	−0.02	−0.76	−0.33	−0.18	1.23
CAG repeat (numbers)	−0.04***	−0.25	0.02	−0.36**	−0.52
SARA score	−0.59****	−0.57****	−0.62****	−0.59****	−0.42****
Tremor [c]	−1.71***	−2.82	−3.83****	−1.03	−0.93

Abbreviations: UHDRS = Unified Huntington's Disease Rating Scale; SCA = Spinocerebellar ataxia; SARA = Scale for Assessment and Rating of Ataxia.

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.005$,

**** $p < 0.001$.

[a] All regression coefficients and *p*-value were calculated in the linear regression model, adjusting for age of first visit, gender, CAG repeat, and neurological symptom

[b] Men = 0, Women = 1

[c] No tremor = 0, tremor = 1