Published in final edited form as:

Parkinsonism Relat Disord. 2018 July ; 52: 24–29. doi:10.1016/j.parkreldis.2018.03.011.

Unaffected First-Degree Relatives of Essential Tremor Cases Have More Imbalance Than Age-Matched Control Subjects

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Abstract

Background—Endophenotypes are measurable clinical characteristics that may be present in individuals with increased risk for disease (e.g., unaffected family members). Endophenotypes are useful; they may clarify diagnosis in genetic studies and foster the development of animal models. In recent years, problems with balance and mild gait ataxia have been associated with essential tremor (ET). We compared gait and balance of first-degree relatives of ET cases (FD-ET) to that of age-matched controls (Co).

Methods—One-hundred-ninety FD-ET and 68 Co, none of whom reported tremor or were diagnosed with ET, underwent a standardized assessment of gait and balance.

Results—FD-ET reported more near-falls in the past year ($p = 0.015$) and lower balance confidence according to the Activities of Balance Confidence (ABC-6) Scale ($p = 0.03$). The specific ABC-6 items for which FD-ET reported lower balance confidence than Co were being bumped into by people while walking ($p = 0.006$) and walking outside on icy sidewalks ($p = 0.007$). On videotaped neurological examination, FD-ET were able to stand in the tandem position

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Conflicts of Interest:

None of the authors has any conflicts of interest.

Authors' Contributions:

Conception and design of study; analysis and interpretation of data; drafting/editing manuscript; final approval of work (EDL).

Analysis and interpretation of data; drafting/editing manuscript; final approval of work (J.P.).

Acquisition of data; drafting/editing manuscript; final approval of work (J.H.M., A.D.C., R.H.).

Conception and design of study; interpretation of data; drafting/editing manuscript; final approval of work (P.F.L.).

for fewer seconds than were Co ($p = 0.048$). The differences between FD-ET and Co, although statistically significant, were clinically mild.

Conclusion—FD-ET reported more near-falls in the past year and a reduction in balance confidence; additionally, ability to maintain tandem stance was impaired compared to Co. These data suggest a more pervasive abnormality of cerebellar dysfunction than previously conceived, extending beyond ET cases themselves and manifesting in mild form in their unaffected family members.

Keywords

Essential tremor; Epidemiology; Genetics; Endophenotype; Gait; Balance

Introduction

Essential tremor (ET) is the most prevalent tremor disorder [1]. The disease is often familial [2]; indeed, first-degree relatives of ET cases are five times more likely to develop ET than are members of the population [3].

Endophenotypes are measurable clinical or biological characteristics that are found more often in individuals with the disease than in the general population. They may be present before the onset of disease and in individuals with increased risk for the disease (e.g., unaffected family members). In addition to furthering genetic analysis, endophenotypes can clarify diagnosis and foster the development of animal models [4]. In movement disorders research, endophenotypes have been studied the most in patients and families with dystonia [5] but they have also been studied in patients with Tourette syndrome [6] and more broadly in other neurological [7] and psychiatric [8] illnesses.

Relatives of ET cases are more likely to exhibit mild tremor than are relatives of control subjects [9, 10], indicating the burden of ET extends beyond the boundaries of the clinically-defined disease, and partially expressed forms of ET are abundant in ET families. In recent years, ET has been associated with a range of clinical features aside from tremor [11]. For example, problems with balance and a mild gait ataxia have been documented in numerous studies [12]. The basis for these problems is not clear, but is likely to be a result of abnormal cerebellar function [13]. Whether these features associated with ET occur in a mild form in unaffected family members is not known.

In this study, we compared gait and balance of first-degree relatives of ET cases (FD-ET) to that of age-matched controls (Co). We hypothesized that FD-ET might exhibit more deficits in gait and balance, albeit mild, than Co. If this were the case, it would serve to strengthen the scientific notion that gait and balance difficulties are associated with ET and, furthermore, it would have implications for the conduct of genetic studies. More broadly, it would strengthen the notion that there may be a pre-tremor phase of illness in ET [14]. Studies of the presymptomatic and early stage of neurodegenerative diseases are pivotal for an advanced understanding of these disorders and for the development of preventive strategies aimed at postponing the clinical onset of these diseases [15]. Therefore, it is

important to identify the earliest and most sensitive clinical signs and biological markers that herald the onset of the illness [15].

Methods

Introduction

FD-ET and their spouses (i.e., Co) were screened for enrollment in an environmental epidemiological study of ET (May 2016 – present) [16].

ET cases had been ascertained from study advertisements to the membership of the International Essential Tremor Foundation, membership in current ET research studies at Yale University, and the clinical practice of the Yale Movement Disorders Group [16].

Screening process for unaffected FD-ET

The screening process for unaffected FD-ET was as follows. First, ET cases informed the investigator of all reportedly unaffected living first-degree relatives age ≥40. With permission, these family members were contacted by telephone. During this telephone call, they were consented (using a protocol approved by the Yale University Institutional Review Board) and interviewed. During the interview, a 12-item tremor screening questionnaire [17] was administered and they were asked about a prior diagnosis of ET. They also completed and mailed four hand-drawn spirals (two right, two left), which were rated by a senior movement disorder neurologist (E.D.L.) using the following scale: 0, 0.5, 1, 1.5, 2, 3 (see definitions and examples in Louis et al) [18].

These FD-ET were initially categorized as unaffected if they met each of the following criteria: (1) they did not report tremor during the 12-item telephone-administered tremor screening questionnaire [17], (2) they had never been assigned an ET diagnosis by a treating physician, and (3) each of their four screening spirals were assigned scores <2.0.

In-person clinical evaluation of FD-ET

FD-ET were invited for an in-person clinical evaluation if initially categorized as unaffected. The evaluation was conducted by trained interviewers in enrollees' homes and included questionnaires (e.g., demographics, tremor features, medical history, medications). The number of reportedly affected first-degree relatives was defined as the genetic load. The Cumulative Illness Rating Scale (CIRS) (range = 0–42 [maximum co-morbidity]) [19], a measure of medical co-morbidity, was administered; this assessed the presence and severity (none = 0, mild = 1, moderate = 2, severe = 3) in 14 body systems. Depressive symptoms were assessed using the Beck Depression Inventory, for which 21 items were rated from 0–3 (total score = 0–63 [maximal symptoms])[20].

The interviewer administered the six-item Activities of Balance Confidence (ABC-6) Scale [21]. The scale asked enrollees to self-rate their confidence in performing functional activities without losing balance or becoming unsteady during a range of situation-specific activities (e.g., walking outside on icy sidewalks). The ABC has been shown to have excellent utility in evaluating balance-related confidence, and scores for each item range from 0–100 (completely confident). The interviewer also asked FD-ET to indicate how

many falls they had had during the past year. Falls were defined as “an event which results in a person coming to rest inadvertently on the ground or supporting surface, and other than as a consequence of a violent blow, loss of consciousness or sudden onset of paralysis.” [22] The interviewer also asked about the number of near-falls (i.e., when subjects felt they were going to fall but did not actually fall) they had had in the past year [22].

The in-person evaluation also included a videotaped neurological examination [23], which included a detailed assessment of postural, kinetic, intention and rest tremors, as well as dystonia and other movement disorders [24]. E.D.L. reviewed all videotaped examinations, and the severity of postural and kinetic arm tremors was rated on 12 examination items using a reliable rating scale [25]. As reviewed [18, 26], ratings were 0, 0.5, 1.0, 1.5, 2, 3 and 4; these resulted in a total tremor score (range = 0 – 46 [maximum]) [24].

An assessment of tandem gait was performed during the study visit and was videotaped so that the number of mis-steps could be counted later by E.D.L. Tandem gait was explained and demonstrated to enrollees; they were carefully instructed to walk placing one foot directly in front of the other, being careful to touch toe to heel with each step. They could choose their own line (i.e., a line was not drawn or placed on the floor). The number of mis-steps (i.e., steps to the side) during a single 10-step trial was counted. Enrollees were also asked to stand in the tandem position, with the dominant foot in front, and the number of seconds (range = 0 – 10) without falling to the side was counted (E.D.L.).

FD-ET were re-evaluated for a potential ET diagnosis based on review of questionnaires and videotaped neurological examination data. Diagnoses of ET were assigned based on published diagnostic criteria (moderate or greater amplitude kinetic tremor during three or more activities or a head tremor in the absence of PD or another known cause [e.g., medication-induced tremor, tremor from hyperthyroidism]) [23, 25, 27].

Final inclusion of FD-ET

FD-ET were included in these analyses if they were initially categorized as unaffected (see above) and if they were NOT diagnosed with ET based on the in-person evaluation.

Parallel procedure for screening and evaluating Co

Co were also screened, if available. Each then underwent the same screening process, in person questionnaire, and videotaped examination. They were included in these analyses if (1) they were initially categorized as unaffected, (2) reported no family history of ET, and (3) they were NOT diagnosed with ET during the in-person evaluation.

Final sample

We screened 451 individuals of whom 336 were initially categorized as unaffected. We further excluded 44 who were diagnosed with ET based on published diagnostic criteria and another 34 who were considered to have borderline ET – that is, they did not fully meet strict diagnostic criteria for ET (defined above) based on the in-person evaluation but were nonetheless considered by the study clinician to have clinical features that aligned them more with ET than normal [28]. Hence, the final sample was 258.

Study power

Using pilot data on tandem stance (mean = 9.6 ± 1.8 seconds) from the first 50 enrolled Co, our sample size provided 96.4% power to detect as little as a 10% reduction in tandem stance in FD-ET. Using pilot data on ABC-6 total score (mean = 530.9 ± 65.2) from our first 50 enrolled Co, our sample size provided >99% power to detect as little as a 10% reduction in ABC-6 score in FD-ET. However, given the wide standard deviations in number of falls and tandem gait, the study was not well powered to detect such small differences in these outcomes.

Statistical analyses

For continuous variables, normality was assessed (Kolmogorov Smirnov test); when the distribution was not normal ($p < 0.05$), non-parametric tests were used (e.g., Mann-Whitney test, Spearman's r). We compared FD-ET to Co in terms of demographic and clinical features (Table 1) using Student's t tests, Mann Whitney tests, chi-square tests and Fisher's exact tests.

Data on current medications were used to create a variable ("medications that could predispose to balance issues or falls") that captured information on number of medications that (1) could directly affect gait and balance (e.g., sedating medications, psychoactive medications associated with balance problems [e.g., anti-convulsants]) or (2) could predispose to lower blood pressure/syncope or hypoglycemia/syncope with resultant falls (e.g., blood pressure medications, medication used to treat diabetes mellitus).

To determine whether gait or balance difficulty correlated with genetic load (i.e., the number of reportedly affected first-degree relatives) in FD-ET, we used Spearman's correlation coefficients to examine the correlations between genetic load and each of our gait and balance variables. We also used Spearman's correlation coefficients to examine the correlations between gait and balance variables and between these variables and other variables. We stratified total tremor score into quartiles, and examined our gait and balance variables across these quartiles in FD-ET (Kruskal-Wallis test).

Results

There were 258 individuals (190 FD-ET, 68 Co) who belonged to 169 and 64 families, respectively. Hence, in large measure, individuals were not from the same families.

FD-ET and Co were similar in age and most other demographic factors (e.g., education, race, language, cigarette smoker); however, they differed by gender ($p < 0.001$, Table 1). As expected, the genetic load was higher in the FD-ET group ($p < 0.001$, Table 1). The total tremor score was higher in FD-ET than Co ($p = 0.015$, Table 1).

By history, FD-ET reported more near-falls in the past year ($p = 0.015$) and lower balance confidence according to the ABC-6 score ($p = 0.03$, Table 1). The specific ABC-6 items for which FD-ET reported lower balance confidence than Co were: being bumped into by people while walking (84.9 ± 24.1 [median = 90.0] vs. 92.1 ± 14.3 [median = 100], $p =$

0.006) and walking outside on icy sidewalks (64.0 ± 25.7 [median = 70.0] vs. 73.3 ± 23.2 [median = 80], $p = 0.007$). For the remaining items, the two groups did not differ.

On videotaped neurological examination, FD-ET were able to stand in the tandem position for fewer seconds than were Co ($p = 0.048$, Table 1). Nearly all (95.5%) Co were able to stand in tandem for the full 10 seconds; by contrast, only 86.0% of FD-ET were able to do so; stated conversely, 14.0% of FD-ET were unable to stand in tandem for the full 10 seconds compared with only 4.5% of Co (i.e., the inability to stand for a full ten seconds was three-times more likely among FD-ET than Co) (chi-square test = 4.23, $p = 0.04$).

Overall, the difference between FD-ET and Co was modest. For example, the median number of near-falls in the past year, though different in the two groups, was 1 in FD-ET and 0 in Co. Co were able to maintain tandem stance on average for 9.6 seconds; for FD-ET, this was 9.0 seconds. The median ABC-6 scores differed by 10 of 600 possible points, also pointing to a small difference.

The mean number of falls reported in the past year was 0.3 in FD-ET and 0.2 in Co, and the mean number of steps to the side during tandem gait (videotaped neurological examination) was 0.9 in FD-ET vs. 0.5 in Co; these comparisons did not reach statistical significance (Table 1, p values = 0.24 and 0.10, respectively).

FD-ET and Co did not differ with respect to the number of prescription medications taken, the burden of medical comorbidity (i.e., CIRS score), or BDI scores (Table 1); hence, these factors could not have accounted for the observed differences in gait and balance variables between the two groups.

We also assessed the number of medications that could predispose to balance issues or falls, and FD-ET and Co did not differ with respect to this variable (Table 1). The number of medications that could predispose to balance issues or falls was not correlated with any of the gait and balance variables in Co. In FD-ET, it was only weakly associated with balance confidence (Spearman's $r = -0.17$, $p = 0.02$) but not with near-falls in the past year (Spearman's $r = 0.02$, $p = 0.83$) or duration of tandem stance (Spearman's $r = -0.06$, $p = 0.40$). After removing all FD-ET and Co taking a medication that could predispose to balance issues and falls, the magnitude of reduction in median balance confidence in FD-ET vs. Co remained similar to that observed in the entire sample of all FD-ET and Co.

We also separately examined the 14 CIRS subscores (cardiac, vascular, respiratory, eyes/ears/nose/throat, upper gastrointestinal tract, lower gastrointestinal tract, hepatic, renal, genito-urinary, musculoskeletal, neurological, hypertension, endocrine, malignancy); FD-ET and Co did not differ with respect to any of these either (all p values >0.17). Of all of these types of diseases, musculoskeletal diseases could manifest with gait or balance issues; however, FD-ET and Co did not differ with respect to these (Table 1). Furthermore, the musculoskeletal disease subscores were not correlated with number of near-falls in the past year, balance confidence or duration of tandem stance in FD-ET (Spearman's r , all $p >0.05$) or Co (Spearman's r , all $p >0.05$). FD-ET and Co did differ by gender (Table 1); however, none of the gait or balance variables differed across genders in FD-ET or in Co, indicating

that gender could not have confounded the association between gait and balance variables and group.

We stratified total tremor score into quartiles, and examined our gait and balance variables across these quartiles in FD-ET (Kruskal-Wallis test) (Table 2); greater tandem gait difficulty and greater tandem stance difficulty, and marginally lower balance confidence, were seen in individuals with more tremor.

We examined the correlations between genetic load and each of our gait and balance variables; there were no associations (all p values > 0.22 , range = $0.22 - 0.75$).

The ABC-6 total score correlated well within FD-ET with the number of falls reported in the past year (Spearman's $r = -0.34$, $p < 0.001$) and the number of seconds without falling to the side during tandem stance (Spearman's $r = 0.27$, $p < 0.001$).

Some individuals were from the same families. To assess whether this affected our results, we performed a sensitivity analysis in which we only included the first enrollee in each family (i.e., 169 of 190 FD-ET and 64 of 68 Co), and compared gait and balance variables in FD-ET vs. Co. These results were similar to those of the main analysis that included all 190 FD-ET and 68 Co (data not shown).

Discussion

We performed a standardized assessment of more than 250 individuals using a combination of self-reported, functionally-based, and objective measures of gait and balance, comparing FD-ET to age-matched Co. None self-reported tremor or met criteria for ET on examination. We found that FD-ET reported more near-falls in the past year and a reduction in balance confidence; on examination, they had more difficulty maintaining tandem stance. These deficits in gait and balance, though present, were mild.

In movement disorders research, endophenotypes have been examined most carefully in patients and families with adult-onset dystonia [5], in which deficits in temporal discrimination have been described. In families of patients with Tourette syndrome, symmetry (e.g., evening up) and disinhibition (e.g., echolalia) are considered endophenotypes [6]. Endophenotypes have also been described in families with epilepsy [7, 29]. As such, endophenotypes have been identified for a wide range of neurological disorders. In psychiatry as well, endophenotypic manifestations have been well-described [8].

Overall, the difference between FD-ET and Co was modest. For example, the median number of near-falls in the past year, though different in the two groups, was only 1 in FD-ET and 0 in Co. Co were able to maintain tandem stance on average for 9.6 seconds; for FD-ET, with was 9.0 seconds. The median ABC-6 total scores differed by 10 out of 600 possible points, also pointing to a small difference. That these differences were small is not surprising; there is no evidence in the clinical research literature that family members of ET patients experience clinically-significant, reportable deficits in gait and balance. The differences we report here are of a subclinical nature. Nonetheless, they are differences.

Is there a cut-off that can be used to distinguish an endophenotype of ET from normal? That is, can we use these data to identify a certain threshold of gait or balance difficulty that is not likely to be normal and which is more likely than not to be a marker for an ET gene carrier? It is difficult to derive from these data such rules that could inform genetic studies. We found that 14% of FD-ET were unable to stand in tandem for the full 10 seconds compared with only 4.5% of Co. The only individuals who were unable to stand in tandem for the full 10 seconds and whose ABC score for “walking outside on icy sidewalks” was <40 were FD-ET, of whom there were 11. Clearly, additional work in larger cohorts is needed in order to make useful statements discriminatory for gene-finding studies.

When we stratified total tremor score into quartiles, we found that greater tandem gait difficulty and greater tandem stance difficulty, and marginally lower balance confidence, were seen in individuals with more tremor. This observation further suggests that this gait and balance difficulty may be a marker for individuals who are at risk for developing ET or who are slowly transitioning into ET. It also indicates that cerebellar dysfunction may begin to arise pre-clinically (i.e., before onset of substantial tremor).

This study should be interpreted within the context of certain limitations. We enrolled more than 250 individuals. Using pilot data on tandem stance, we determined that our sample size provided 96.4% power to detect as little as a 10% reduction in tandem stance in FD-ET. Using pilot data on ABC-6 score, our sample size provided >99% power to detect as little as a 10% reduction in ABC-6 score in FD-ET. However, given the wide standard deviations in number of falls and tandem gait, the study was not well powered to detect such small differences in these outcomes. Hence, it is possible that the differences between the two groups (i.e., marginally better performance in Co than FD-ET, Table 1) could have reached statistical significance with a larger sample. Future studies with expanded samples would be valuable. Second, we did not utilize a computerized instrumented walkway to quantify gait parameters, as this is difficult to transport into the field. Third, the movement disorders neurologist was not blinded to subject type (FD-ET vs. Co) during the videotape review. Thus, it is possible that reviewer bias could have influenced the results. We do not think this was a problem because several outcomes were by self-report (e.g., number of falls, number of near-falls, balance confidence). Even the outcomes that were assessed based on the videotaped neurological examination were simple timed outcomes rather than qualitative or ordinal-distributed reviewer-assigned metrics. Also, the significant correlation between reviewer-assigned and self-report measures (the number of seconds without falling to the side during tandem stance correlated with ABC-6 total score, Spearman's $r = 0.27$, $p < 0.001$) further indicates that reviewer-assigned scores were not biased. Strengths of the study included the use of a combination of self-reported, functionally-based, and objective measures of gait and balance impairment. Second, we carefully collected data on potential confounding factors (e.g., the number of prescription medications taken, the burden of medical comorbidity, depressive symptoms), which we considered in our analyses. Finally, all enrollees underwent a detailed in-person assessment, which included a videotaped neurological examination, which was examined by a senior movement disorders neurologist.

Conclusions

In summary, FD-ET reported more near-falls in the past year and a reduction in balance confidence; additionally, ability to maintain tandem stance was impaired compared to Co. These data raise the possibility of a more pervasive abnormality of cerebellar dysfunction than previously conceived, extending beyond ET cases themselves and manifesting in mild form in their unaffected family members.

Acknowledgments

Funding:

This study was supported by the National Institutes of Health, R01 NS094607. Dr. Louis has received research support from the National Institutes of Health: NINDS #R01 NS094607 (principal investigator), NINDS #R01 NS085136 (principal investigator), NINDS #R01 NS073872 (principal investigator), NINDS #R01 NS085136 (principal investigator) and NINDS #R01 NS088257 (principal investigator). He has also received support from the Claire O'Neil Essential Tremor Research Fund (Yale University).

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- We studied gait and balance in unaffected first-degree relatives of ET cases.
- Unaffected first-degree relatives of ET cases reported more near-falls than controls.
- They also reported a reduction in balance confidence.
- Their ability to maintain tandem stance was impaired compared to controls.
- Mild cerebellar dysfunction extends beyond ET cases to their unaffected relatives.

Table 1

Demographic and clinical features of 190 FD-ET vs. 68 Co

	FD-ET n = 190	Co n = 68	Significance
Current age in years	56.7 ± 9.7	56.4 ± 9.6	0.79 ^a
Female gender	128 (67.4)	23 (33.8)	<0.001 ^b
Education in years	16.6 ± 2.9 [16.0]	16.7 ± 3.6 [17.0]	0.84 ^c
White race	183 (96.3)	65 (95.6)	0.73 ^d
English language	186 (97.9)	65 (95.6)	0.38 ^d
Current cigarette smoker	4 (2.1)	0 (0.0)	0.58 ^d
Number of prescription medications	1.9 ± 2.0 [1.0]	2.5 ± 2.8 [2.0]	0.50 ^c
Number of medications that could predispose to balance issues or falls	0.6 ± 1.0 [0.0]	0.7 ± 1.0 [0.0]	0.67 ^c
CIRS score	4.2 ± 3.3 [4.0]	4.0 ± 3.8 [3.0]	0.50 ^c
Musculoskeletal disease			0.41 ^b
None	136 (71.6)	55 (80.9)	
Mild problem	36 (18.9)	10 (14.7)	
Moderate problem	16 (8.4)	3 (4.4)	
Severe problem	2 (1.1)	0 (0.0)	
BDI	4.5 ± 4.5 [3.0]	4.5 ± 4.6 [3.0]	0.83 ^c
Genetic load ^I	1.4 ± 0.9 [1.0]	0.0 ± 0.0 [1.0]	<0.001 ^c
Total tremor score	6.7 ± 2.2 [6.5]	5.85 ± 2.3 [5.5]	0.006 ^c
Number of falls in past year	0.3 ± 0.7 [0.0]	0.2 ± 0.6 [0.0]	0.24 ^c
Number of near-falls in past year	2.8 ± 10.8 [1.0]	2.4 ± 12.5 [0.0]	0.015 ^c
ABC-6 total score	494.1 ± 128.3 [540.0]	530.7 ± 74.0 [550.0]	0.03 ^c
Tandem gait (number of steps to the side)	0.9 ± 1.7 [0.0]	0.5 ± 1.2 [0.0]	0.10 ^c
Tandem stance (number of seconds without falling to the side)	9.0 ± 2.6 [10.0]	9.6 ± 1.9 [10.0]	0.048 ^c

Values are mean ± standard deviation [median] or number (percent).

^aStudent's t test.^bChi-square test.

^c Mann-Whitney test.

^d Fisher's exact test.

ABC (Activities of Balance Confidence), BDI (Beck Depression Inventory), CIRS (Cumulative Illness Rating Scale).

^l The number of reportedly affected first-degree relatives was defined as the genetic load.

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Table 2

Balance stratified by quartiles of tremor severity in 190 FD-ET

	TTS Q1	TTS Q2	TTS Q3	TTS Q4	Significance
Number of falls in past year	0.4 ± 0.7 [0.0]	0.1 ± 0.4 [0.0]	0.4 ± 0.7 [0.0]	0.4 ± 0.9 [0.0]	0.15 ^a
Number of near-falls in past year	2.6 ± 7.5 [0.0]	1.1 ± 1.8 [0.0]	2.2 ± 3.8 [1.0]	7.1 ± 22.4 [1.0]	0.35 ^a
ABC-6 total score	506.3 ± 94.0 [520.0]	528.3 ± 84.1 [550.0]	463.9 ± 153.1 [522.0]	444.8 ± 183.9 [500.0]	0.10 ^a
Tandem gait (number of steps to the side)	0.5 ± 0.9 [0.0]	0.4 ± 0.8 [0.0]	1.3 ± 2.4 [0.0]	1.6 ± 2.4 [0.0]	0.04 ^a
Tandem stance (number of seconds without falling to the side)	9.3 ± 2.1 [10.0]	9.8 ± 1.3 [10.0]	8.2 ± 3.4 [10.0]	8.7 ± 3.0 [10.0]	0.04 ^a

Values are mean ± standard deviation [median].

^aKruskal-Wallis test.

ABC (Activities of Balance Confidence). TTS (total tremor score).

TTS Q1 = total tremor score quartile 1 (total tremor score = 5).

TTS Q2 = total tremor score quartile 2 (total tremor score = 5.5 – 6.5).

TTS Q3 = total tremor score quartile 3 (total tremor score = 7 – 8.5).

TTS Q4 = total tremor score quartile 4 (total tremor score > 8.5).