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Tremor and Other Hyperkinetic Movements

Article

Mental Status Test Scores are Inversely Correlated with Tremor Severity: A Study of 161 Elderly Essential Tremor Cases

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Abstract

Background: There is an increasing awareness that patients with essential tremor (ET) may exhibit non-motor features, including cognitive dysfunction. Yet there are surprisingly few data in ET on the association, if any, between cognitive dysfunction and motor dysfunction (i.e., tremor severity). Establishing links between the cognitive and motor features of ET would imply that the two share a common underlying pathogenic process. Recent neuroimaging data support this notion.

Methods: ET cases were enrolled in a clinical–pathological study at Columbia University Medical Center, New York. The Folstein Mini-Mental State Examination (FMMSE) and Modified Mini Mental Status Examination (mMMSE) were administered. Action tremor was rated with a total tremor score (TTS).

Results: There were 161 ET cases (mean age 83.9 ± 5.7 years, median FMMSE 28, median mMMSE 50). The FMMSE and mMMSE were inversely correlated with the TTS ($r=-0.22$, $p=0.005$; and $r=-0.17$, $p=0.029$). The association, while statistically significant, was modest in magnitude. In linear regression models that adjusted for age, gender, and education, the association between cognitive test scores and TTS remained robust ($p<0.001$). After excluding 68 (42.2%) cases taking ET medications with potential cognitive side effects, results remained unchanged.

Conclusions: Each of the two cognitive test scores was associated with tremor severity such that greater cognitive dysfunction occurred in cases with more marked tremor. These data support recent imaging data, which suggest that the cerebellar neurodegeneration underlying ET may be involved in the expression of cognitive symptoms in ET.

Keywords: Essential tremor, non-motor, mental status, tremor severity, clinical

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Introduction

There is an increasing awareness that patients with essential tremor (ET) may exhibit non-motor features, with cognitive dysfunction being prominent among these.[1,2] Most of the emerging literature has focused on case–control differences in cognitive test scores.[2–5] By contrast, there are few data on the association, if any, between cognitive dysfunction and motor dysfunction (i.e., tremor severity), and the few data that do exist are conflicting.[5–8] The mechanistic basis for the cognitive dysfunction in ET is unclear, as is the basis for the tremor itself. Establishing links between the cognitive and motor features of ET would imply that the two share a common underlying pathogenic process. Recent imaging data suggest that the cerebellar neurodegeneration, which may underlie ET, may be involved in the expression of cognitive symptoms in ET.[9]

Methods

ET cases were enrolled in an ongoing clinical–pathological study at Columbia University Medical Center (CUMC), New York.[10,11] The study enrolled ET cases as future brain donors. ET cases were ascertained through a variety of mechanisms including advertisements

on the International Essential Tremor Foundation website and newsletters, advertisements on the Tremor Action Network website, and our research study's website (www.essentialtremor.us). ET cases were recruited throughout the United States of America and were not restricted to New York. As of March 2009, more than 300 ET cases had expressed interest in enrollment. Beginning in March 2009, we began enrolling cases at a rate of approximately 7 per month, with selection based on age, starting with the oldest, and targeting to enroll 175 cases. To date, 165 ET cases have been enrolled, of whom complete data were available on 161.

Upon enrollment, each case signed a written informed consent form, approved by the CUMC institutional ethics committee, and then underwent a standardized in-person evaluation in their home by the same trained tester. The in-person evaluation included the collection of demographic and clinical data using structured questionnaires. To assess cognition, we administered the Folstein Mini-Mental State Examination (FMMSE; range 0–30 [no impairment])[12] and the Modified Mini Mental Status Examination (mMMSE, range 0–57 [no impairment]).[13] Depressive symptoms were assessed using the Beck Depression Inventory, for which 21 items were rated from 0 to 3 (total score 0–63 [maximal symptoms]).[14] Medical co-morbidity was assessed with a Cumulative Illness Rating scale (total score = 0–42 (severe comorbidity).[15]

During a videotaped examination, postural and kinetic tremor in each arm was tested, and then rated (range 0–4 for each item, E.D.L.), and a total tremor score (TTS, range 0–46) was assigned to each case.[15] The diagnosis of ET was reconfirmed in each ET case using research diagnostic criteria (moderate or greater amplitude kinetic tremor observed during three or more activities or a head tremor, in the absence of Parkinson's disease).[15,16]

Analyses were carried out using SPSS (version 19; Chicago, Illinois). The TTS was normally distributed (Kolmogorov–Smirnov $z=0.89$, $p=0.40$) but the FMMSE and mMMSE were not (respective Kolmogorov–Smirnov $z=2.12$, $p<0.001$; and $z=1.57$, $p=0.01$). Therefore, non-parametric tests (e.g., Spearman's rho, Mann–Whitney test, Kruskal–Wallis test) were used when assessing the FMMSE and mMMSE. In unadjusted and then adjusted linear regression models, we assessed the association between the TTS (independent variable) and the log-transformed FMMSE (dependent variable). Parallel unadjusted and then adjusted linear regression models were performed using the log-transformed mMMSE as the dependent variable.

Results

The 161 ET cases had a mean age of 83.9 ± 5.7 years (Table 1). The median FMMSE =28 and the median mMMSE =50. Eleven (6.8%) participants had a FMMSE score <24, indicating more significant cognitive impairment.

Both the FMMSE and the mMMSE scores were inversely correlated with age (i.e., older age was associated with more cognitive difficulty, Table 2). The FMMSE scores were higher in females than males (Table 2). The mMMSE scores were not associated with gender but were marginally associated with education (i.e., higher educational attainment was marginally associated with less cognitive difficulty, Table 2). The FMMSE and MMSE scores were correlated with one another (Spearman's $r=0.78$, $p<0.001$, Table 2). The TTS was not associated with age, gender, or education (Table 2).

Table 1. Demographic and Clinical Characteristics of 161 ET Cases

	ET (n=161)
Age (years)	83.9 ± 5.7, 72–102
Women	98 (60.9%)
Education[1]	
No degree	5 (3.1%)
High School diploma	50 (31.4%)
Associates degree	14 (8.8%)
Bachelor's degree	43 (27.0%)
Master's degree	31 (19.5%)
Doctorate degree	16 (10.1%)
FMMSE score	27.0 ± 2.7 [28.0], 11–30
mMMSE score	49.3 ± 5.8 [50.0], 18–57
Beck Depression Inventory score	9.4 ± 6.9
Cumulative Illness Rating Scale score	10.3 ± 5.3
Age of tremor onset (years)	42.1 ± 22.7
Tremor duration (years)	41.6 ± 21.9
Total tremor score	24.7 ± 7.5 [24.0], 4.5–46

Values either represent mean ± standard deviation [median], minimum –maximum, or they represent numbers (percentages).
Abbreviations: ET, essential tremor; FMMSE, Folstein Mini-Mental State Examination; mMMSE, Modified Mini Mental Status Examination.
[1]Data missing on two participants.

Both the FMMSE and the mMMSE were inversely correlated with the TTS ($r=-0.22$, $p=0.005$; and $r=-0.17$, $p=0.029$, respectively), such that higher tremor scores (more severe tremor) were associated with lower cognitive test scores (more cognitive difficulty) (Table 2). While the association was statistically significant, the magnitude of the association was modest.

In an unadjusted linear regression model, TTS was inversely associated with the log-transformed FMMSE (beta $=-0.002$, $p<0.001$). In a linear regression model that adjusted for age in years,

Table 2. Correlations Between Demographic/Clinical Characteristics and Mini Mental State Examination Scores and Tremor Scores in 161 ET Cases

	Correlation (r) Between Characteristic and FMMSE Score *or* FMMSE Score within Stratum of Each Characteristic	**Correlation (r) Between Characteristic and mMMSE Score *or* mMMSE Score within Stratum of Each Characteristic**	**Correlation (r) Between Characteristic and TTS *or* TTS within Stratum of Each Characteristic**
Age (years)	$r_s=-0.38$, $p<0.001$	$r_s=-0.30$, $p<0.001$	$r_p=0.04$, $p=0.61$
Gender			
Women	27.4 ± 2.7 [28.0]	49.3 ± 5.8 [50.5]	24.3 ± 7.5
Men	26.4 ± 2.6 [27.0]	49.7 ± 4.9 [50.0]	25.4 ± 7.5
	MW=2.98, p=0.003	MW=0.05, p=0.96	T=0.96, p=0.34
Education			
No degree	26.6 ± 1.5 [26.0]	48.8 ± 4.2 [49.0]	27.8 ± 9.8
High School	26.5 ± 3.1 [28.0]	47.5 ± 7.1 [49.0]	25.1 ± 6.8
Associates degree	27.5 ± 2.1 [27.0]	49.0 ± 5.1 [49.0]	26.3 ± 6.9
Bachelor's degree	27.3 ± 2.6 [28.0]	50.5 ± 5.3 [52.0]	24.7 ± 7.9
Master's degree	27.0 ± 2.8 [28.0]	49.9 ± 5.3 [51.0]	23.6 ± 9.2
Doctorate degree	27.4 ± 1.9 [27.5]	51.0 ± 3.8 [51.5]	23.4 ± 4.9
	KW=3.66, p=0.60	KW=7.86, p=0.16	ANOVA=0.55, p=0.74
FMMSE score	Not applicable	$r_s=0.78$, $p<0.001$	$r_s=-0.22$, $p=0.005$
mMMSE score	$r_s=0.78$, $p<0.001$	Not applicable	$r_s=-0.17$, $p=0.029$
Beck Depression Inventory score	$r_s=-0.09$, $p=0.30$	$r_s=-0.13$, $p=0.11$	$r_p=0.13$, $p=0.11$
Cumulative Illness Rating Scale score	$r_s=-0.04$, $p=0.66$	$r_s=-0.04$, $p=0.61$	$r_p=-0.004$, $p=0.97$
Age of tremor onset[1]	$r_s=-0.10$, $p=0.20$	$r_s=-0.13$, $p=0.12$	$r_p=-0.20$, $p=0.01$
Tremor duration[1]	$r_s=0.03$, $p=0.75$	$r_s=0.08$, $p=0.30$	$r_p=0.21$, $p=0.008$

Abbreviations: ANOVA, analysis of variance; ET, essential tremor; FMMSE, Folstein Mini-Mental State Examination; KW, Kruskal-Wallis test; mMMSE, Modified Mini Mental Status Examination; MW, Mann–Whitney test; T = t test; TTS, total tremor score.
Values are either correlation coefficients (r) and p values, or mean ± standard deviation [median]. Correlation coefficients are either Spearman's rho (r_s) or Pearson's rho (r_p).
[1]In years.

gender, and level of education, the TTS (beta =−0.002, p<0.001) and age (beta =−0.002, p<0.001) were inversely associated with the log-transformed FMMSE. Further adjusting for the Beck Depression Inventory score and Cumulative Illness Rating Scale Score did not change the results (for the TTS, beta =−0.002, p<0.001).

In an unadjusted linear regression model, TTS was inversely associated with the log-transformed mMMSE (beta =−0.002, p=0.002). In a linear regression model that adjusted for age in years, gender, and level of education, the TTS (beta =−0.002, p=0.002) and age (beta =−0.003 p<0.001) were inversely associated with the log-transformed mMMSE. Further adjusting for the Beck Depression Inventory score and Cumulative Illness Rating Scale Score did not change the results (for the TTS, beta =−0.002, p=0.007).

Sixty-eight (42.2%) cases were on an ET medication with potential cognitive side effects (e.g., mysoline, benzodiazepines). When these 68 were excluded, the results were similar: the FMMSE and mMMSE

were inversely correlated with the TTS ($r=-0.28$, $p=0.006$; and $r=-0.24$, $p=0.002$, respectively).

Discussion

In this study we examined the possible links between tremor severity and performance on cognitive testing in elderly ET cases. Two cognitive test screens were used. We found that each of our cognitive test scores was associated with our clinical measure of tremor severity, such that greater cognitive dysfunction was associated with more marked arm tremor. While the association was statistically significant, the magnitude of the association was modest. The association persisted in adjusted regression models.

Most of the emerging literature in ET has focused on case–control differences in cognitive test scores.[2–5] The data on any associations between cognitive dysfunction and motor dysfunction are limited.[5–8] A study in the United States of 101 ET cases (mean age 72 ± 9.8 years) undergoing evaluation for tremor surgery reported that there were no correlations between cognitive measures and tremor severity, with all p-values >0.10, although the details of the analyses were not reported.[8] A study of 18 ET cases (mean age 66.1 ± 12.3 years) attending a neurosurgical clinic in the United States similarly reported that tremor severity was not correlated with cognitive deficits, although the details of those analyses were not reported either.[6] By contrast, a study in Turkey assessed 16 ET cases using a comprehensive neuropsychological test battery and reported their results in detail.[5] The authors found a correlation between tremor severity and number of errors on the Wisconsin Card Sorting Test (a test of Executive Function) and the Hooper Visual Organization Test (a test of visuospatial function), with r-values ranging from 0.51 to 0.76 for these correlations.[5] Yet there was no reported correlation between tremor severity and a wide range of other tests of attention, memory, language, or planning.[5] That study differed from ours in the sense that the ET cases were very young (29.6 ± 10 years [18–52 years]).[5] Finally, a study in Korea assessed 47 ET cases (mean age 68.2 ± 7.3 years) with a detailed neuropsychological test battery that included a Korean version of the Mini-Mental State Examination.[7] Their sample was a mixed sample that included 17 ET cases without dementia, 21 ET cases with mild cognitive impairment, and nine ET cases with dementia. Tremor severity correlated marginally with the Mini-Mental State Examination score ($r=-0.249$, $p=0.092$), a result that was similar to our own, and with a small number of other cognitive test items (the Korean version of the Boston Naming test, delayed recall).[7]

Several of these studies, including our own, suggest that there are links between the cognitive and motor features of ET. Establishing links between the cognitive and motor features of ET would imply that the two share a common underlying pathogenic process, which could be the structural white and gray matter changes in the cerebellum noted in some studies.[18] Indeed, a study in Italy used functional neuroimaging to assess 15 ET patients and 15 controls while they executed a verbal working memory task. They tested whether ET patients displayed abnormal activations of the cerebellum and other areas typically engaged in working memory (e.g., dorsolateral prefrontal cortex, parietal lobules). ET patients showed greater cerebellar response (crus I/lobule VI) than controls during attention-demanding working memory trials, and altered functional connectivity between crus I/lobule VI and regions implicated in focusing attention and in generating distracting self-related thoughts. They concluded that the cerebellar neurodegeneration underlying ET is reflected in abnormal communications between key regions responsible for working memory, and that adaptive mechanisms (e.g., enhanced response of crus I/lobule VI) occur to limit the expression of cognitive symptoms in ET.[9]

This study was not without limitations. First, our cases were very old, so we may not be able to generalize our results to younger ET cases. Nevertheless, the study in Turkey that enrolled the younger sample also detected an association between cognitive and motor features in ET.[5] Second, aside from the issue of generalizability discussed above, the issue of confounding by age was addressed by including age as a covariate in our analyses. Third, the cognitive testing relied on a very small number of handwritten items (copying figures), and tremor may have resulted in shaky drawings. This would not have influenced our results. The grading of these drawings as correct vs. incorrect was not based on the apparent presence vs. absence of oscillations but rather, on the ability to reproduce the appropriate visual–spatial relationships between constituent lines and shapes. Fourth, cerebrovascular disease, and its effects on the brain, is a confounding factor that we were not able to take into consideration. Brain imaging would have allowed us to have done so. Finally, the measures of cognitive function that we used were mental status test scores rather than detailed neuropsychological test batteries. Despite this limitation, significant associations were apparent.

The study had a number of strengths. First, the sample size that we used ($n=161$), was larger than that of any prior study. Second, given the advanced age of participants, a full range of mini mental status test scores was observed and included. Third, we carefully considered in our analyses the possible effects of a range of confounding factors (e.g., age, gender, education, medications, depressive symptoms).

Each of the two cognitive test scores was associated with tremor severity such that greater cognitive dysfunction occurred in cases with more marked arm tremor. These data support recent imaging data, which suggest that the cerebellar neurodegeneration, which may underlie ET, may be involved in the expression of cognitive symptoms in ET. Future studies of specific cerebellar cognitive dysfunctions and their associations with tremor severity could provide information of additional pathophysiological relevance.

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