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Functional Correlates of Lower Cognitive Test Scores in Essential Tremor

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Abstract

Background—Although motor features have been the defining element of essential tremor (ET), lower neurocognitive test scores are increasingly being recognized. However, the clinical correlates, if any, of these lower test scores remain largely unexplored.

Objective—To determine whether cognitive test scores in ET have any functional correlates.

Methods—The Modified Mini Mental Status Examination (MMSE), Katz Activities of Daily Living (ADL) scale and Lawton Instrumental (I) ADL scale were administered to 95 cases.

Results—The Katz ADL score (rho = 0.26, p = 0.01) and Lawton IADL score (rho = 0.32, p = 0.001) were correlated with MMSE scores, such that poorer cognitive performance indicated greater dysfunction. Furthermore, cognitive test scores were a better predictor of functional disability than was tremor severity.

Conclusions—Poorer cognitive performance in ET was associated with greater functional deficit. Cognition should enter the clinical dialogue with ET patients as an issue of clinical significance.

Keywords

essential tremor; cognition; dementia; mini mental status; functional disability; epidemiology; Alzheimer's disease

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Author Contributions

Elan D. Louis: Research project conception, organization and execution; manuscript writing (writing the first draft and making subsequent revisions).

Introduction

Essential tremor (ET) is among the most prevalent movement disorders.[1, 2] While the motor features of ET have been the defining element of the disorder, there is a growing appreciation of the existence of non-motor features as well.[3–5] In an increasing number of studies, mild cognitive problems (i.e., significantly lower than expected scores on measures of complex auditory and visual attention, verbal fluency, and immediate recall) are being observed in ET cases,[6–12] and associations between ET and both prevalent and incident dementia have been reported in recent population-based studies in Spain and New York.[13–15]

Several of the reports showing lower neurocognitive test scores in ET were case-control studies,[7, 10, 11] demonstrating that the observed cognitive changes were beyond those seen with typical aging. The reported deficits have generally been 1 – 1.5 standard deviations below normal,[5] a magnitude suggesting that they reflect mild impairment. In a population-based study,[11] forgetfulness was reported in marginally more ET patients than controls, which raised the possibility that the cognitive deficits in ET may not be entirely subclinical. Yet the clinical correlates, if any, of these diminished test scores in ET have largely been unexplored so it remains unclear whether they have any clinical significance. If cognitive changes in ET were clinically inconsequential, I hypothesized that there would be no functional correlates. If, on the other hand, these cognitive changes have some clinical significance, one might detect an association with increased functional disability.

Methods

95 ET cases were enrolled in the Columbia University Assessment of Disability in ET study;[16, 17] by design, they were ascertained from two distinct sources: (1) the Washington Heights-Inwood community in northern Manhattan, New York, and (2) the Center for Parkinson's Disease and Other Movement Disorders at Columbia University Medical Center (CUMC), New York, NY. The ET cases from the community had mild ET that was for the most part untreated;[18] complementing these were the CUMC cases with more severe and disabling tremor. Detailed description of the case ascertainment has been reported.[16, 17] Briefly, community-based cases were identified from the Washington Heights Inwood Genetic Study of ET (1995 – 2000), a health study based in northern Manhattan, and patients at CUMC were selected at random from a computerized patient database (1997 – 2000).

After signed written informed consent, demographic and medical questionnaires were administered by a trained tester. The Modified Mini Mental Status Examination (MMSE, range = 0 – 57 [highest performance])[19] was administered. This reliable and valid test is an expanded measure of global cognitive status based on the Folstein Mini-Mental State Exam,[20] and includes assessments of orientation (range = 0 – 10), registration and digit span (range = 0 – 13), attention and calculation (range = 0 – 7), general knowledge (range = 0 – 5), recall (range = 0 – 3), language (range = 0 – 17), and construction (range = 0 – 2). Two assessments of function were administered. The Katz Activities of Daily Living (ADL) scale[21] is a 6-item scale that assesses basic functions (bathing, dressing, toileting, transfers, continence, feeding). A score of 6 indicates full independence, and 0, full dependence. The Lawton Instrumental ADL (IADL) scale has been used to assess more complex skills (ability to use telephone, shopping, food preparation, housekeeping, laundry, public transportation, responsibility for taking medications, and ability to handle finances). Total scores range from 0 to 23 (completely independent). Women are scored on all functional domains, whereas for men, the domains of food preparation, housekeeping, laundering are traditionally excluded (total score range = 0 – 14).

The tester videotaped a tremor examination,[22, 23] including postural arm tremor and five tests of kinetic tremor in each arm (12 tests total). Videotapes were reviewed by a senior neurologist (E.D.L.) who rated tremor (0 – 3) during each test. Each participant was assigned a total tremor score (range = 0 – 36).

Neither the Katz ADL nor the Lawton IADL scores were normally distributed (Kolmogorov-Smirnov p values <0.001); therefore, non-parametric tests were used when evaluating these variables (e.g., Mann Whitney test, Spearman's rho). In linear regression analyses, the outcome variable (Katz ADL score or Lawton IADL score in different models) was log-transformed. In these models, the MMSE score was the independent variable. Analyses began with unadjusted models. Then multivariate analyses were performed that included covariates if they had been associated at the $p < 0.05$ level with either MMSE or the outcome variable in univariate analyses.

Results

Mean Katz ADL score and Lawton IADL scores are shown (Table). The Katz ADL and Lawton IADL scores were correlated with one another (rho = 0.37, p = 0.001) (Table). Greater dysfunction (i.e., lower Katz ADL and Lawton IADL scores) was associated with older age and older age of tremor onset. Lower Katz ADL scores were associated with more severe tremor (higher total tremor score). Women had lower Katz ADL scores than men (Table); while the Lawton IADL scores were higher in women, this was because the score included three more items in women. When these three items were excluded, the Lawton score was lower in women (12.1 ± 3.0, median = 14 [women] vs. 13.4 ± 1.6, median = 14 [men], p = 0.02).

Both the Katz ADL (rho = 0.26, p = 0.01) and Lawton IADL (rho = 0.32, p = 0.001) scores were correlated with the MMSE score (poorer cognition correlated with greater dysfunction) (Table, Figure). Stratifying by case type yielded similar results (for Lawton IADL, rho [community cases] = 0.35, p = 0.026 and rho [clinical cases] = 0.52, p < 0.001; for Katz ADL, rho [community cases] = 0.24, p = 0.15 and rho [clinical cases] = 0.29, p = 0.036). Furthermore, cognitive test scores were a greater predictor of functional disability than was the total tremor score (e.g., in Table, the correlation between the Lawton IADL score and the MMSE score = 0.32 [p = 0.001] whereas the correlation between the Lawton IADL score and the total tremor score = −0.11 [p = 0.29]).

MMSE scores were stratified into tertiles (tertile 3, MMSE ≥56; tertile 2, MMSE = 51 – 55; tertile 1, MMSE score ≤50); the Lawton IADL score decreased (lower function) with decreasing MMSE score tertile (tertile 3 = 19.3 ± 4.3 [median = 22], tertile 2 = 17.2 ± 5.0 [median = 15], tertile 1 = 14.6 ± 6.1 [median = 14], p = 0.007).

MMSE scores were subdivided into assessments of orientation, registration and digit span, attention and calculation, general knowledge, recall, language, and construction items. Correlations with Lawton IADL and Katz ADL were most robust for registration and digit span, attention and calculation, recall, and language (Table).

In linear regression analyses, MMSE score was associated with log Katz ADL score (unadjusted beta = 0.01, p < 0.001; and beta adjusting for age, gender, and age of tremor onset = 0.01, p < 0.001). Including total tremor score in an adjusted model yielded a similar result (beta = 0.01, p < 0.001). Similarly, in linear regression analyses, MMSE score was associated with log Lawton IADL score (unadjusted beta = 0.008, p < 0.001; adjusted beta = 0.01, p < 0.001). Including total tremor score in an adjusted models yielded a similar result (beta = 0.01, p < 0.001).

Discussion

Rather than having no clinical correlate, cognitive test score results in ET were clearly associated with several measures of functional disability. Stratifying by case type (community-ascertained vs. clinic cases) yielded similar results. Furthermore, cognitive test scores were a better predictor of functional disability than was the total tremor score. These data suggest that cognitive decline in ET has a clinical-functional correlate.

Studies of patients with frank dementia (Alzheimer's disease or Dementia with Lewy Bodies) have enrolled patients with MMSE scores ≤30 (mean = 20.5 – 22.1),[24, 25] scores which were not observed in the current set of ET cases (mean = 51.4, range = 33 – 57). The MMSE scores in these ET cases therefore likely reflected only mild impairment in cognition. Yet even in this setting, there were clear functional correlates.

The Lawton IADL, in particular, was correlated with the MMSE score. The correlation coefficient (rho) was 0.32, indicating that, in our sample, the MMSE score explained approximately 10% of the variance in the Lawton IADL score. On the one hand, this value is somewhat small and the remaining 90% of the variance in the Lawton IADL score was likely due to age, gender and other factors. On the other hand, this value (10%) is relatively large. The total tremor score (rho = −0.11) explained only 1% of the variance in the Lawton IADL score, indicating that cognitive test scores were a better predictor of functional disability in this sample of ET cases than was their total tremor score. This underscores the importance of non-motor features in a disease that has traditionally been viewed as a strictly motor disorder.

The basis for the cognitive dysfunction in ET is not clear. Studies that noted an association between ET and dementia reported that the majority of demented ET cases had Alzheimer's disease.[13–15] A recent postmortem study of ET [26] found slightly more Alzheimer's type pathology in ET cases than age-matched controls. Alternatively, other pathological mechanisms (e.g. cerebrovascular) might explain this association. The mechanistic basis for the dementia as well as milder cognitive problems in ET clearly merits additional study.

Cognitive test scores correlated more strongly with the Lawton IADL than the Katz ADL score. There are several possible explanations. First, the Katz ADL scale (range = 0 – 6) has a far more limited range than the Lawton IADL scale (0 – 23), making it more difficult to establish correlations. Second, the Lawton IADL scale measures activities of daily living in a more nuanced manner than the Katz ADL scle, thereby allowing it to detect more subtle alterations in function that might be the result of smaller cognitive changes.

This study had limitations. The cognitive testing was limited to the modified MMSE. Nonetheless, even with this constraint, a correlation between this relatively simple cognitive measure and several functional scales was detectible. One would expect that the use of a more comprehensive test battery would further delineate the nature of this correlation. Second, both functional measures had ceiling effects (e.g., see Figure). This likely biased these results towards the null hypothesis, making it more difficult to detect correlations. This study had several strengths. Two widely-used, validated measures of functional ability were employed. ET cases came from two sources, one of which was from a population, thereby facilitating the replication of the main findings in two distinct patient subgroups.

These results have clinical implications. They suggest that cognitive issues should enter the clinical dialogue with ET patients rather than being viewed merely as normal features of aging or problems of no clinical-functional importance. Further study is needed of the prevalence, clinical correlates and mechanistic basis of the cognitive disorder associated with ET.

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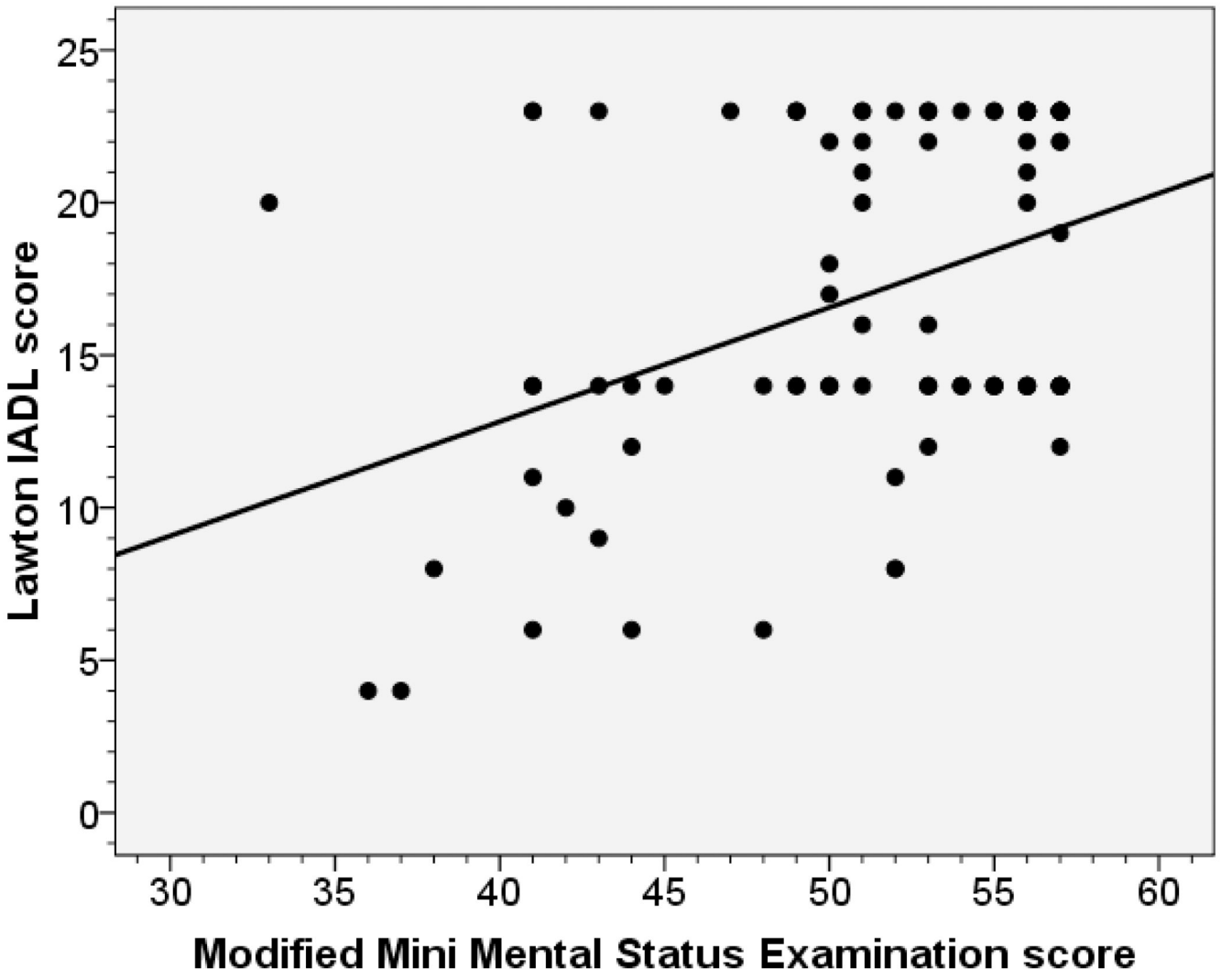

Figure.
The MMSE score was correlated with the Lawton IADL score in 95 ET cases (rho = 0.32, p = 0.001, poorer cognition correlated with greater dysfunction).

Table

Clinical Characteristics and Correlates of Katz ADL and Lawton IADL Scores in 95 ET Cases

	Clinical Characteristics of 95 ET Cases[a]	**Katz ADL Score[b]**	**Lawton IADL Score[b]**
Age (years)	70.0 ± 15.6	rho = −0.25, p = 0.02	rho = −0.21, p = 0.04
Gender			
Men	37 (38.9)	5.9 ± 0.5, median = 6	13.4 ± 1.6, median = 14[d]
Women	58 (61.1)	5.6 ± 1.2, median = 6	19.4 ± 5.8, median = 23[d]
		p = 0.03[c]	p = <0.001[c]
Education (years)	13.5 ± 5.1	rho = 0.16, p = 0.13	rho = 0.15, p = 0.15
Duration of tremor (years)	20.2 ± 20.0	rho = 0.03, p = 0.81	rho = 0.14, p = 0.21
Age of tremor onset (years)	49.4 ± 23.8	rho = −0.20, p = 0.07	rho = −0.28, p = 0.009
Takes medication for ET			
Yes	28 (29.5)	5.6 ± 1.2, median = 6	17.0 ± 5.8, median = 6.5
No	67 (70.5)	5.7 ± 0.9, median = 6	17.1 ± 5.4, median = 14
		p = 0.88[c]	p = 0.88[c]
Total tremor score	19.2 ± 7.8	rho = −0.23, p = 0.03	rho = −0.11, p = 0.29
MMSE score	51.4 ± 5.8 (range=33–57)	rho = 0.26, p = 0.01	rho = 0.32, p = 0.001
Orientation	9.8 ± 0.5 (range=8–10)	rho = 0.14, p = 0.17	rho = 0.28, p = 0.007
Registration	11.9 ± 1.3 (range=7–13)	rho = 0.32, p = 0.002	rho = 0.33, p = 0.001
Attention/Calculation	6.2 ± 1.7 (range=0–7)	rho = 0.31, p = 0.002	rho = 0.30, p = 0.003
General Knowledge	3.8 ± 1.4 (range=1–5)	rho = 0.05, p = 0.61	rho = 0.20, p = 0.06
Recall	2.2 ± 1.1 (range=0–3)	rho = 0.23, p = 0.03	rho = 0.25, p = 0.015
Language	16.0 ± 1.5 (range=11–17)	rho = 0.20, p = 0.06	rho = 0.27, p = 0.007
Construction	1.5 ± 0.7 (range=0–2)	rho = 0.11, p = 0.28	rho = 0.12, p = 0.24
Katz ADL score	5.7 ± 1.0 (range = 0 – 6)	Not applicable	rho = 0.37, p = 0.001

	Clinical Characteristics of 95 ET Cases[a]	Katz ADL Score[b]	Lawton IADL Score[b]
Lawton IADL score[d]	17.1 ± 5.5 (range = 4–23)	rho = 0.37, p = 0.001	No applicable

[a] Values are mean ± SD or number (percent).

[b] Some cells show the correlation between the clinical characteristic (e.g., age, tremor duration) and the ADL score. Other cells show the mean ± SD ADL score in strata of the disease characteristic (e.g., ADL score in men vs. women; ADL score in medication takers vs. non-takers).

[c] Mann-Whitney test.

[d] Women are scored on all functional domains, whereas for men, the domains of food preparation, housekeeping, laundering are traditionally excluded (total score range = 0 – 14).