Published in final edited form as:

Eur J Neurol. 2011 October ; 18(10): 1251–1257. doi:10.1111/j.1468-1331.2011.03374.x.

Frailty in Elderly Persons with Essential Tremor: A Population-Based Study (NEDICES)

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Abstract

OBJECTIVES—Essential tremor (ET), one of the most prevalent neurological diseases, has been associated with a variety of co-morbidities and, in some studies, a modest increase in risk of mortality. The mechanisms underlying this possible increased mortality have yet to be explored, although one possibility is increased frailty. Frailty has not been studied in ET and our objective was to address this gap in knowledge. We hypothesized that frailty would be greater in ET cases than controls.

METHODS—A 20-item frailty score assessed co-morbid conditions, number of medications and functional activity. The frailty score was compared in 237 non-demented elderly ET cases and 3,903 non-demented age-matched controls from a population-based study in central Spain.

RESULTS—The frailty score was higher in ET cases than controls (8.6 ± 5.2 vs. 6.8 ± 4.6 , $p < 0.001$). Stratifying the frailty score into quartiles and tertiles similarly revealed case-control differences (both $p < 0.001$). The frailty score also increased with age ($r = 0.25$, $p < 0.001$), was higher in women than men ($p = 0.02$), was correlated with subjective rating of health status ($r = 0.42$, $p < 0.001$) and was inversely correlated with body weight ($r = -0.06$, $p < 0.001$) and hours/day that participants performed moderate or intensive physical activities ($r = -0.16$, $p < 0.001$).

CONCLUSION—ET cases had increased frailty compared to their counterparts without this disease. Whether this increased frailty is a contributor to the increased risk of mortality that has been observed in some studies is a question that deserves further scrutiny.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

Keywords

Essential tremor; neurological; frailty; morbidity; mortality

INTRODUCTION

Essential tremor (ET), one of the most prevalent neurological diseases [1], is characterized by progressively worsening action tremor [2]. In a growing number of case-control studies, ET has also been associated with a variety of co-morbidities (e.g., hearing impairment, cognitive difficulty, depression, changes in gait and balance) [3–9]. In the only prospective controlled study of mortality, ET cases had a 45% increased risk of mortality compared to controls [10]. The mechanisms underlying this possible increased mortality are not known and have not been explored. One potential explanation is increased frailty. Frailty has not been studied in ET so it is not currently known whether the elderly with ET are more frail than age-matched controls.

Frailty is a term that is used to denote a multidimensional syndrome of loss of reserves (energy, physical ability, cognition, health) that gives rise to vulnerability [11–13]. The syndrome has a predilection for the elderly [14]. The accurate identification of frailty in elderly patients has prognostic implications [14]; frailty confers a higher risk for falls, disability, hospitalization, and mortality [14–17]. There are also therapeutic implications as patients with frailty may benefit from exercise intervention [14,18]. Furthermore, identification of frail patients can help to plan preventative measures or institutional care resources [11]. Frailty is a potentially modifiable vulnerability state and therefore is a major clinical and research focus in geriatric medicine [19]. Hence, there are a variety of reasons to study frailty in ET.

This study used a population-based sample of 237 non-demented elderly ET cases, comparing them to 3,903 non-demented age-matched normal controls. We hypothesized that frailty would be greater in ET cases than age-matched controls.

METHODS

Study Population

Data were derived from the Neurological Disorders in Central Spain (NEDICES) study, a longitudinal, population-based survey of the prevalence, incidence, and determinants of major age-associated conditions of the elderly, including ET, Parkinson's disease (PD) and dementia [3,20]. Detailed accounts of the study population and sampling methods have been published [3,20]. The study population was composed of elderly subjects, ≥ 65 years old, living in three communities in central Spain (Las Margaritas, Lista and Arévalo). Of 5,914 eligible subjects, 5,278 were enrolled at baseline. Ethics committee approval was obtained (University Hospital "12 de Octubre" and University Hospital "La Princesa") and written informed consent was obtained from participants upon enrollment.

Study Evaluation

Detailed accounts of the study assessments have been published [3,20]. Face-to-face evaluations were performed at baseline (1994–1995) and follow-up (1997–1998). The current analyses utilized data derived from the baseline evaluation.

During the baseline evaluation, data were collected on demographics, current medications, current medical conditions (e.g., circulatory problems, visual problems), and, as reported previously [8], the presence of depressive symptoms (the question, "do you suffer from

depression?”). Stroke diagnoses were later confirmed based on medical record review and general neurological examination. Participants were asked to subjectively rate their health status using 5 categories: 1 (very good), 2 (good), 3 (normal), 4 (bad), 5 (very bad). They were also asked a question about limitation in daily activities: “Do some of the chronic conditions or diseases that you have limit or make difficult your current daily activities, such as going out of your house, visiting your friends, doing housework or going to a show?” Participants also reported the number of hours per day that they perform moderate or intensive physical activities.

As previously-reported [21], a Spanish adaptation of the Pfeffer Functional Activities Questionnaire was administered to participants. The Pfeffer Functional Activities Questionnaire [22] assesses 10 common activities that require complex cognitive and social functioning. Reported performance on these 10 tasks is rated from 0 (normal) to 3 (dependent).

As described [3,23], a neurological examination was performed, comprised of a general neurological examination, a tremor examination (three manual tasks to assess postural and kinetic tremors, including sustained bilateral arm extension, bilateral finger–nose–finger maneuver with a minimum of six repetitions with each arm and the drawing of an Archimedes spiral with the dominant arm), and the motor portion of the Unified Parkinson’s Disease Rating Scale (UPDRS) [24]. Body weight was recorded (in kg).

All participants also underwent a neuropsychological test battery [3]. As part of that battery, a 37-item Mini-Mental State Examination (37-MMSE) was administered [25]. This was a Spanish adaptation of the standard MMSE [26].

Participants were diagnosed as having ET if they had an action tremor of the head, limbs, or voice without any recognizable cause. The tremor had to be of gradual onset and either present for at least 1 year, or accompanied by a family history of the same disorder (at least one first-degree relative affected). Participants with tremor related to alcohol withdrawal, hyperthyroidism, anxiety, PD, antidopaminergic drug intake, lithium therapy, or other known causes of tremor, were excluded. ET cases identified by 1 neurologist were subsequently examined by 2 different neurologists. That is, the participants were classified as having ET only when the 3 neurologists agreed [27]. Diagnostic criteria for PD [28] and dementia [20] have been described elsewhere.

Evaluating Frailty

Frailty may be assessed using a considerable number of methods and there is no single, generally-accepted approach. Among the common methods used to operationally define frailty are rules-based methods, counting and summing patients’ clinical deficits, and methods based on more detailed clinical interviews [11]. We used a combination of a clinical questionnaire and a summing the number of clinical deficits, working with the variables available in this particular database. We used the following 20 items, which were combined to form a frailty score:

1. 14 co-morbid conditions (except for stroke, all based on self-report and each coded as present [1] or absent [0]): stroke, circulatory problems, visual problems, cataracts, hearing problems, osteoarthritis, osteoporosis, hip fracture, cancer, anemia, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, heart disease.
2. Depressive symptoms (i.e., answered “yes” to the question “do you suffer from depression?”, and coded as 1 [yes] or 0 [no]).

3. Number of medications. This was a continuous variable.
4. Self-reported limitation in daily activities, coded 1 (yes) or 0 (no).
5. Three items from the Spanish adaptation of the Pfeffer Functional Activities Questionnaire[21]: (i) Going outside alone; (ii) traveling out of the neighborhood, driving, arranging to take a bus; and (iii) shopping alone for clothes, household necessities or groceries. Each of the three items was coded from 0 (normal) to 3 (dependent). These three items were selected because they are relevant markers of frailty.

Final Selection of Participants

There were 5,278 participants (256 ET and 5,022 controls). We excluded 81 (1.5%) participants with prevalent PD, as our intention was to study participants with another tremor disorder (i.e., ET). We further excluded 293 participants with prevalent dementia, as the validity of their reported co-morbidity may be questioned, and 202 participants with incomplete data, leaving 4,702 potential participants, including 237 ET cases and 4,465 controls, who differed by age. Hence, for the final sample, controls were frequency-matched to ET cases based on age, resulting in 4140 participants, including 237 ET cases and 3,903 controls who were of nearly identical age (Table 1). The final sample of 4,140 was similar to the base sample of 5,278 participants in terms of gender (2,374 [57.3%] vs. 3,040 [57.6%] women, chi-square = 0.06, $p = 0.80$), education (556 [13.4%] vs. 708 [13.4%] with secondary or higher education, chi-square = 0.00, $p = 0.98$) and, on average, they were 0.4 years older (74.7 ± 6.2 vs. 74.3 ± 7.0 years, $t = 2.89$, $p = 0.004$).

Statistical Analyses

Analyses were performed in SPSS (Version 18.0, Chicago, IL). Demographic and clinical characteristics were compared using Student's t tests, chi-square tests and Pearson's rho. In several analyses, the frailty score was stratified into quartiles or tertiles.

RESULTS

The 237 ET cases were similar to the 3,903 controls in terms of age, gender, education, marital status and all other demographic variables (Table 1).

ET cases and controls were compared with respect to each of the 20 items in the frailty score and they differed with respect to one-half (i.e., 10) of the 20 items (Table 2). These ten items included 1 co-morbidity previously associated with ET (hearing problems) and depressive symptoms (previously associated with ET) as well as 3 co-morbidities not previously associated with ET (circulatory problems, osteoarthritis, chronic obstructive pulmonary disease), number of medications, self-reported limitation in daily activities, and all 3 functional activity items.

The frailty score ranged from 0–31 (6.9 ± 4.6), with 95% of participants scoring in the 0–16 range, and 75% scoring in the 0–9 range. When the variable “number of medications” was removed, the range was only 0–21, with 95% of participants scoring in the 0–12 range and 75% in the 0–6 range.

The mean frailty score was 26.5% higher in ET cases than controls (8.6 ± 5.2 vs. 6.8 ± 4.6 , $t = 5.27$, $p < 0.001$). Stratifying the frailty score into quartiles and then tertiles also revealed case-control differences, with a larger proportion of ET cases having scores in higher strata and a larger proportion of controls having scores in the lower strata (both $p < 0.001$, Table 3).

The frailty score increased with age ($r = 0.25$ $p < 0.001$). The frailty score was higher in women than men (7.1 ± 4.7 vs. 6.7 ± 4.6 , $t = 2.27$, $p = 0.02$) even though the two has nearly identical ages (74.8 ± 6.3 vs. 74.6 ± 6.2 , $t = 0.86$, $p = 0.39$). In analyses that stratified ET cases and controls by gender, the frailty scores were higher in cases of both genders than controls of both genders ($p = 0.001$ among men and $p < 0.001$ among women, Table 3).

ET has previously been associated with several co-morbidities (hearing impairment, cancer, depressive symptoms). In an analysis in which these three items were removed, (i.e., creating a 17-item rather than 20-item frailty score), the case-control difference persisted ($p < 0.001$, Table 3). We further subdivided the 17-item frailty score into two sub-scores: 12 co-morbidities (none previously associated with ET) and the 5 remaining items (medications, self-reported limitation, 3 functional items). The case-control differences persisted in each of these two sub-scores (both $p < 0.001$). These analyses support the notion that there may be an additional frailty syndrome in ET that is above and beyond what has been described previously. Stratifying ET cases based into subgroups that reflected tremor severity (newly vs. previously diagnosed ET, unmedicated vs. medicated ET, and short vs. longer durations) revealed that all strata of ET cases differed from controls (Table 3).

The frailty score correlated with subjective rating of health status (i.e., frailer participants had poorer subjective health ratings, $r = 0.42$, $p < 0.001$), and inversely with body weight (i.e., frailer participants weighed less, $r = -0.06$, $p < 0.001$) and inversely with the number of hours per day that participants performed moderate or intensive physical activities (i.e., frailer participants were less physically active, $r = -0.16$, $p < 0.001$).

Although we excluded participants with dementia, milder cognitive impairment may have been present and may have affected the validity of self-reported measures of co-morbidity. In an analysis in which we excluded all participants with 37-MMSE scores in the bottom tertile (37-MMSE score ≤ 27), results were similar, with the 119 remaining ET cases having higher frailty scores than the 1,993 remaining controls (8.0 ± 4.7 vs. 6.5 ± 4.3 , $t = 3.41$, $p = 0.001$). We also explored whether the frailty index was just a proxy for depression; we excluded all 924 participants who reported depressive symptoms. In these analyses, the frailty score remained lower in the remaining 146 ET cases than 3,070 controls (7.3 ± 4.7 vs. 6.0 ± 4.2 , $t = 3.13$, $p = 0.002$).

DISCUSSION

In this population-based study, elders with ET were compared to their counterparts without this disease. Frailty scores were significantly higher in ET cases than controls, with the contributors to that increase including a variety of co-morbidities and self-reported limitations and dysfunctions. Although ET has previously been associated with several co-morbidities (hearing impairment, cancer, depressive symptoms), case-control differences in other co-morbidities, medications, self-reported limitation, and functional items occurred beyond these previously described co-morbidities, suggesting that there may be an additional frailty syndrome in ET that is above and beyond what has been described previously. Frailty was a marker of a variety of other health measures and health outcomes including lower body weight (i.e., frailer participants weighed less), number of hours per day that participants were able to perform moderate or intensive physical activities (i.e., frailer participants were less physically active), and subjective rating of health status (i.e., frailer participants had poorer subjective health ratings), further demonstrating that the syndrome was an indicator of the broader health condition.

The case-control difference, though significant, was an absolute difference of 1.8 points. In relative terms, this represented a 26.5% increase in ET. To put this finding in context, other

community-based studies indicate that every 2.5% increase in the frailty index in the elderly is associated with a 4% increased risk of mortality [29], so that with a 26.5% increase in the frailty index, one might expect a 42.4% increased risk of mortality. Of interest is that the one prospective study of mortality in ET revealed a 45% increased risk of mortality [10]. The increased frailty in ET is possibly one more indicator that ET is not “benign”. The increased vulnerability to hearing impairment, cognitive difficulty, depression, and changes in gait and balance observed in studies over the past decade [3–9], are further indicators that this disease is not the benign condition it was viewed as a decade ago.

There are many definitions of frailty [13], which indicates that this syndrome has been difficult to fully conceptualize and understand. Yet there is some consensus that it is a physiological syndrome that results from a cumulative decline across multiple physiological systems, and which is characterized by decreased physiological reserve, diminished resistance to stressors, and increased vulnerability to adverse outcomes.

There are few data on mortality in ET. Prospective, controlled data may be found in a single study, which demonstrated a mild yet significantly increased risk of mortality in ET [10]. Further controlled studies are needed. Whether the possible increased risk of mortality in ET is a function of greater frailty is not known, although numerous studies of other elderly groups do indicate that increased frailty is a predictor of increased mortality [11,17]. The presumed mechanism is a decreased physiological reserve and increased vulnerability to stressors and adverse outcomes.

Our measure of frailty was derived for these particular analyses. The question arises as to its validity. The measure we used included many of the items used by others in their assessments of frailty [11]. The frailty scores correlated with both age (i.e., higher frailty scores were observed in older participants) and gender (i.e., women had higher frailty scores than men), which according to Rockwood [13], is an important feature of a frailty measure. Furthermore, as with other frailty indices [11], the measure included a mix of item-types, including co-morbidities and self-rated health.

This study had several limitations. The presence of co-morbid medical conditions was determined by self-report and not routinely validated by medical record review. Second, there are a number of other contributors to or markers of frailty (esp. physical markers such as gait speed, grip strength, etc) for which data were not collected. Nonetheless, prior studies have shown abnormalities in both gait speed and effective grip in ET [7,30], suggesting that inclusion of these items would likely have further widened the gap between cases and controls.

This study also had several strengths. Ascertainment of cases through doctor’s offices or tertiary referral centers over-selects the most severe and debilitated ET cases. Our population-based design avoided that form of selection bias. Second, the large sample of 237 ET cases and 3,903 controls provided a sample size that was more than adequate to detect case-control differences and avoid Type II error.

In summary, ET cases had increased frailty compared to their counterparts without this disease. Whether this increased frailty is a contributor to the increased risk of mortality that has been observed in some studies is a question that deserves further scrutiny.

Acknowledgments

The NEDICES Study Group included JM Morales, R Gabriel, A Portera-Sánchez, A Berbel, A Martínez-Salio, J Díaz-Guzmán, J Olazarán, J Pardo, J Porta-Etessam, F Pérez del Molino, J Rivera-Navarro, M Alonso, C Gómez, C Saiz, G Fernández, P Rodríguez, F Sánchez-Sánchez and R Trincado.

FUNDING

The NEDICES study was supported by the Spanish Health Research Agency (FIS 93/0773 and 96/1993) and the Spanish Office of Science and Technology. Additional support was obtained through R01 NS042859 and R01 NS039422 from the National Institutes of Health, Bethesda, Maryland. The sponsor's played no role in the design, methods, subject recruitment, data collections, analysis and preparation of this paper.

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TABLE 1

Demographic and Clinical Characteristics of 237 ET Cases and 3,903 Controls

Demographic and Clinical Characteristics	ET cases	Controls	Significance
Age	75.0 ± 6.9	74.7 ± 6.2	0.51 ^A
Female gender	142 (59.9)	2,232 (57.2)	0.41 ^B
Secondary or higher education	32 (13.5)	524 (13.4)	0.97 ^B
Current smoker	26 (11.0)	354 (9.1)	0.33 ^B
Current ethanol user (at least one drink/week)	67 (28.3)	1,048 (26.9)	0.63 ^B
Living situation *			0.31 ^B
Lives alone	42 (20.2)	526 (16.6)	
Lives with one or more people	164 (78.8)	2,580 (81.2)	
Nursing home resident	2 (1.0)	49 (1.5)	
Other	0 (0.0)	23 (0.7)	
Marital status *			0.30 ^B
Single	17 (8.1)	312 (9.7)	
Married or has partner	119 (56.7)	1,908 (59.1)	
Separated or divorced	6 (2.9)	47 (1.5)	
Widowed	68 (32.4)	961 (29.8)	
Number of people living with participant	1.1 ± 1.2	1.1 ± 1.3	0.96 ^A

Values are means ± standard deviations of numbers (percentages).

* n < 4,140 due to missing data.

^A Student's t test,^B chi-square test.

TABLE 2

ET cases vs. Controls with Respect to Each of the 20 Items in the Frailty Score

Items in the Frailty Score	ET cases	Controls	Significance
Stroke	14 (5.9)	167 (4.3)	0.23 ^B
Circulatory problems	98 (41.4)	1,211 (31.0)	0.001 ^B
Visual problems	124 (52.3)	1,924 (49.3)	0.42 ^B
Cataracts	82 (34.6)	1,143 (29.3)	0.08 ^B
Hearing problems	89 (37.6)	1,126 (28.8)	0.004 ^B
Osteoarthritis	163 (69.7)	2,300 (58.9)	0.006 ^B
Osteoporosis	43 (18.1)	602 (15.4)	0.26 ^B
Hip fracture	7 (3.0)	130 (3.3)	0.75 ^B
Cancer	19 (8.0)	254 (6.5)	0.36 ^B
Anemia	30 (12.7)	371 (9.5)	0.11 ^B
Chronic obstructive pulmonary disease	49 (20.7)	609 (15.6)	0.04 ^B
Hypertension	128 (54.0)	2,010 (51.5)	0.45 ^B
Diabetes mellitus	39 (16.5)	629 (16.1)	0.89 ^B
Heart disease	25 (10.5)	403 (10.3)	0.91 ^B
Depressive symptoms	91 (38.4)	833 (21.3)	<0.001 ^B
Number of medications	2.76 ± 2.12	2.28 ± 1.86	0.001 ^A
Self-reported limitation in daily activities	83 (35.0)	731 (18.7)	<0.001 ^B
Going outside alone	0.27 ± 0.73	0.18 ± 0.64	0.04 ^A
Traveling out of the neighborhood, driving, arranging to take a bus	0.60 ± 1.10	0.42 ± 0.95	0.01 ^A
Shopping alone for clothes, household necessities or groceries	0.42 ± 0.91	0.23 ± 0.71	0.001 ^A

Values are means ± standard deviations of numbers (percentages).

For most items, n <4,140 due to missing data.

^A Student's t test,

^B chi-square test.

Bold significance values indicate that p <0.05.

Table 3

Frailty in 237 ET Cases vs. 3,903 Controls

Frailty Scores	ET cases	Controls	Significance
Frailty score	8.6 ± 5.2	6.8 ± 4.6	<0.001^A
Quartiles of frailty score			<0.001^B
Low (score = 0–3)	38 (16.0%)	1,001 (25.6%)	
2 nd (score = 4–6)	52 (21.9%)	1,149 (29.4%)	
3 rd (score = 7–9)	61 (25.7%)	840 (21.5%)	
Highest (score ≥10)	86 (36.3%)	913 (23.4%)	
Tertiles of frailty score			<0.001^B
Low (score = 0–4)	61 (25.7%)	1,383 (35.4%)	
Middle (score 5–7)	48 (20.3%)	1,071 (27.4%)	
High (score ≥8)	128 (54.0%)	1,449 (37.1%)	
Frailty score by gender			
Men	8.2 ± 4.9	6.6 ± 4.5	0.001^A
Women	8.9 ± 5.4	6.9 ± 4.6	<0.001^A
17-Item frailty score ¹	7.8 ± 5.0	6.2 ± 4.3	0.001^A
Frailty score ²			
Previously-diagnosed ET (N=50)	8.2 ± 5.7	6.8 ± 4.6	0.03^A
Newly-diagnosed ET (N = 187)	8.7 ± 5.1	6.8 ± 4.6	<0.001^A
Frailty score ³			
Medicated ET (N = 13)	9.4 ± 3.1	6.8 ± 4.6	0.04^A
Unmedicated ET (N = 224)	8.6 ± 5.3	6.8 ± 4.6	<0.001^A
Frailty score ⁴			
Long Duration ET (N = 114)	8.3 ± 5.0	6.8 ± 4.6	0.001^A
Unmedicated ET (N = 123)	8.9 ± 5.4	6.8 ± 4.6	<0.001^A

Values are means ± standard deviations of numbers (percentages).

^A Student's t test,^B chi-square test.

Bold significance values indicate that p <0.05.

¹ After removal of three items: hearing impairment, cancer, depressive symptoms.² Analysis compared 50 ET cases diagnosed with ET prior to this study to 3,903 controls, and compared 187 ET cases diagnosed during this study to 3,903 controls.³ Analysis compared 13 ET cases who were taking ET medication to 3,903 controls, and compared 224 ET cases who were not taking a medication for ET to 3,903 controls.⁴ Analysis compared 114 ET cases with tremor duration >5 years to 3,903 controls, and compared 123 ET cases with tremor duration ≤5 years to 3,903 controls.