Published in final edited form as:

Eur J Neurol. 2015 February ; 22(2): 384–388. doi:10.1111/ene.12589.

Reduced Body Mass Index in Essential Tremor: A Study of 382 Cases and 392 Matched Controls

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Abstract

Background—There is mounting evidence that essential tremor (ET) is a neurodegenerative disease. Reduced body mass index (BMI) is a clinical feature of many neurodegenerative diseases, yet there has been little documentation of BMI in patients with ET.

Methods—ET cases and controls were enrolled in a study of the environmental epidemiology of ET at Columbia University Medical Center. Weight and height were measured using a standard protocol; BMI was weight (kg)/height in m². Daily calorie count (kcal) was calculated using the Willett Semi-Quantitative Food-Frequency Questionnaire. Tremor severity was assessed with a clinical rating scale (total tremor score, range = 0 – 36).

Results—The 382 ET cases and 392 controls were similar with respect to age, gender and other demographic variables. BMI was lower in ET cases than controls: 26.7 ± 5.0 (median = 26.2) vs. 27.7 ± 5.6 (median = 26.7), $p = 0.03$, despite the fact that the daily caloric intake was marginally higher in ET cases than controls ($p = 0.09$). In ET cases, BMI was not associated with tremor severity (Spearman's $r = -0.02$, $p = 0.66$) but, among younger onset ET cases, longer tremor duration was associated with lower BMI (Spearman's $r = -0.14$, $p = 0.049$).

Conclusions—The lower BMI in ET we observed is consistent with the neurodegenerative hypothesis of ET. The data also suggest that some mechanism other than decreased daily caloric intake or an involuntary movement-related increased burning of calories is likely to account for this case-control difference.

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Disclosure: The authors declare that there are no conflicts of interest and no competing financial interests.

Keywords

essential tremor; body mass index; epidemiology; clinical; neurodegeneration

Introduction

Essential tremor (ET) is among the most common neurological diseases [1-3], with patients cared for by a broad array of medical practitioners. Although disease mechanisms are not well understood, there is growing evidence that ET is neurodegenerative [4-6].

Reduced body mass index (BMI) is a clinical feature of many neurodegenerative diseases, including Parkinson's disease (PD) [7, 8], Huntington's disease [9], and Alzheimer's disease [10]. The mechanism is unclear but is likely multi-factorial: dietary changes, increased caloric consumption due to movement, neuroendocrine disturbances, and/or changes in basal metabolic rate [7, 9, 11]. In PD, weight loss has been associated with an increased risk for pneumonia and shortened life expectancy [7]. A modest increased risk of mortality has been reported in patients with ET, with death from pneumonia being more common than seen in controls [12].

There have been few studies of BMI in ET and, in these studies, the number of patients has been small ($n = 78$ [13] and $n = 89$ [14]). Moreover, the clinical correlates of lower BMI in ET have received scant attention. In addition, the mechanisms are unclear; only one of the two studies presented data on calorie counts, but only in a sub-sample of 40 cases [13]. Hence, the issue has not been exhaustively studied.

Capitalizing on the enrollment of approximately 400 ET cases and an equal number of matched controls in a clinical-epidemiological study in New York, we now (1) compare BMI in cases vs. matched controls, (2) present data on daily caloric intake in all of these subjects, calculated from a food frequency questionnaire, (3) correlate BMI with (a) tremor severity and tremor duration, (b) a variety of other clinical features (e.g., presence of rest tremor, severity of cranial tremor), and (c) a non-motor feature of ET (i.e., cognitive test score). Our overarching goal was to further refine our understanding of the clinical features as well as the biology of this ubiquitous neurological disease.

Methods

Subjects

ET cases were enrolled from 2000 – 2009 in a study of the environmental epidemiology of ET at Columbia University Medical Center (CUMC) [15]. They were adults (age 18 and older) derived from two primary sources: (1) patients whose neurologist was on staff at the Institute or (2) patients who were cared for by their local doctor in the tri-state region (New York, New Jersey, Connecticut) and, as members of the International Essential Tremor Foundation, had read advertisements for the study and volunteered. Prior to enrollment, all cases signed informed consent approved by the CUMC Ethics Committee.

Control subjects were recruited for the same study during this time period. Controls were identified using random digit telephone dialing within a defined set of telephone area codes that were represented by neurological cases (e.g., 212, 201, 203, 516, 718, and 914) within the New York Metropolitan area. Controls were frequency-matched to ET cases based on current age (5 year intervals) and gender; the ratio of controls to cases was ~1:1.

Evaluation

A Telephone Interview for Cognitive Status (TICS, range = 0 – 41 [no deficits]) was administered prior to the in-person study assessment [16], and individuals who scored < 30 were excluded. An in-person structured evaluation was performed during which a trained research assistant administered demographic, medical history, and family history questionnaires. Age of tremor onset and duration of tremor were noted. The questionnaires included items that were socioeconomic indicators (e.g., number of rooms in home/number of people living in home, number of live births [women], and years since last hospitalization). The Cumulative Illness Rating Scale (CIRS) was used to quantify comorbid illness. The CIRS score can range from 0 (no illness) - 42 (severe comorbidity in all 14 systems) [17]. The Willett Semi-Quantitative Food-Frequency Questionnaire was administered [18]. This 20-minute food-frequency questionnaire included questions on frequency of current consumption of 61 foods and on the use of vitamins and mineral supplements. Food frequency data were used to compute mean daily caloric intake (in Kcal). The questionnaire has shown good reliability and validity related to recent nutrient intake [18].

A videotaped neurological examination was performed. This included one test for postural tremor and five for kinetic tremor (pouring, using spoon, drinking, finger-nose-finger, drawing spirals) performed with each arm (12 tests total). A neurologist specializing in movement disorders (E.D.L.) used a reliable [19] and validated [20] clinical rating scale, the Washington Heights-Inwood Genetic Study of ET (WHIGET) tremor rating scale, to rate postural and kinetic tremor during each test: 0 (none), 1 (mild), 2 (moderate), 3 (severe). These ratings resulted in a total tremor score (range = 0 – 36), which is an assessment of postural and kinetic tremor [21]. On videotaped examination, rest tremor was noted as present or absent in a variety of positions (seated, standing, walking) and neck, jaw and voice tremors were coded as present or absent while cases were seated facing the camera. As described elsewhere, a cranial tremor score (range = 0 – 3) was calculated for each subject based on the number of locations (neck, jaw, voice) in which tremor was present on examination [22]. The videotaped examination, as well as the history, were used to confirm the ET diagnosis using published diagnostic criteria (kinetic arm tremor rated 2 during at least 3 tests or head tremor)[21]. None of the ET cases had PD or dystonia.

Weight and height were assessed using a standard protocol. With the subject standing, measurements were taken of body weight to the nearest 0.1 pound using a balance scale designed for field surveys (Scale-Tronix 5600, White Plains, NY). Height was measured to the nearest 0.5 cm using a movable anthropometer (GPM Martin Type, Pfister Inc, Carlstadt, NJ). BMI was calculated as weight in kg divided by the square of height in meters.

Statistical Analyses

Analyses were performed using SPSS (version 21.0). Clinical characteristics of ET cases and controls were compared using Student's t-tests and chi-square (X^2) tests. When variables were not normally distributed (as determined using the Kolmogorov-Smirnov test), a non-parametric test (Mann-Whitney test) was used. In controls, we assessed the association between BMI and demographic and clinical variables using non-parametric tests (Mann-Whitney test and Spearman's correlation coefficient). We stratified BMI into quartiles and, in a logistic regression analysis, we assessed the association between highest vs. lowest BMI quartile in ET cases vs. controls (dependent variable). We also assessed the association between BMI and diagnosis (dependent variable) in a logistic regression model (unadjusted and then adjusting for potential confounders identified in bivariate analyses). We used Spearman's correlation coefficients to assess the association between BMI and demographic and clinical variables. In one analysis, ET cases were stratified based on median age of onset (50.0 years) into two groups, younger-onset vs. older-onset; prior analysis indicate that the two groups differ with respect to biological relationships [23, 24].

Results

The 382 ET cases and 392 controls were similar with respect to age, gender, race and other demographic variables and socioeconomic indicators (Table 1). Among controls, BMI was marginally inversely associated with education (i.e., higher education = lower BMI, Spearman's $r = -0.15$, $p = 0.004$) but not with age (Spearman's $r = 0.03$, $p = 0.61$), unless the age was older than 70 years (Spearman's $r = -0.22$, $p = 0.004$). BMI was lower in women than men (Mann-Whitney $z = 2.25$, $p = 0.024$) but did not differ by race. The daily caloric intake was marginally higher in ET cases than controls (Table 1), although the difference did not reach statistical significance ($p = 0.09$).

BMI was lower in ET cases than controls (Table 1). In a quartiles analysis, controls were 64% more likely to be in the highest vs. lowest BMI quartile than cases (odds ratio [OR] = 1.64, 95% confidence interval [CI] = 1.09 – 2.45, $p = 0.017$). In an unadjusted logistic regression analysis, lower BMI was associated with ET (OR = 0.97, 95% CI = 0.94 – 0.99, $p = 0.01$). After adjusting for age, gender and education in a logistic regression model, OR = 0.96, 95% CI = 0.94 – 0.99, $p = 0.007$. Further adding daily caloric intake to the adjusted model did not change the results: OR = 0.96, 95% CI = 0.94 – 0.99, $p = 0.01$. BMI was lower than 18.5 (i.e., malnourished) in only 6 (1.6%) ET cases and 6 (1.5%) controls ($X^2 = 0.002$, $p = 0.96$).

Approximately 50% of ET cases were taking medications to treat tremor. Some of these medications could have effects on weight and BMI. Therefore, we performed an analysis in which we excluded all ET cases who were taking a medication to treat tremor ($n = 206$). The BMI in the remaining 176 ET cases remained lower than that of 392 controls (26.4 ± 4.5 [median = 25.9] vs. 27.7 ± 5.6 [median = 26.7], Mann-Whitney $z = 2.44$, $p = 0.015$).

In ET cases, there was no correlation between BMI and total tremor score (Spearman's $r = -0.02$, $p = 0.66$). In 57 ET cases with rest tremor, BMI was 26.1 ± 5.1 (median = 25.7) vs. 26.9 ± 5.0 (median = 26.3) among those without rest tremor, Mann-Whitney $z = 0.95$, $p =$

0.34. There was no correlation in ET cases between BMI and cranial tremor score (Spearman's $r = -0.01$, $p = 0.88$). There was no correlation between BMI and TICS score (Spearman's $r = 0.00$, $p = 0.99$).

Although there was no correlation between BMI and tremor duration (Spearman's $r = -0.04$, $p = 0.45$), when the sample was stratified by median age of tremor onset (50.0 years), in younger-onset cases, longer tremor duration was associated with lower BMI (Spearman's $r = -0.14$, $p = 0.049$). In ET cases with a first- or second-degree relative with ET or tremor, BMI was 26.4 ± 4.4 (median = 26.3) vs. 26.9 ± 5.3 (median = 26.1) among those without a family history, Mann-Whitney $z = 1.54$, $p = 0.12$.

Discussion

In this large sample of approximately 800 enrollees, BMI was significantly lower in ET cases than matched controls. The magnitude of the reduction was 3.6%; by comparison, similar or slightly higher reductions of 3 - 9% have been reported in patients with Alzheimer's disease [10] and 7.2% in patients with PD [8]. Furthermore, the daily caloric intake was marginally higher in ET cases than controls, so reduction in caloric intake is not a likely explanation for the observed lower BMI in ET cases. Adjusting for potential confounders did not change our main finding either. Finally, among younger onset cases, longer tremor duration was associated with lower BMI.

We assessed the correlations between BMI and a variety of clinical factors. BMI was not associated with several motor features aside from action tremor in the arms (i.e., presence/absence of rest tremor, cranial tremor) nor was it associated with a test of cognition (TICS score). The latter result suggests that it is not cognitive impairment, observed in ET [25], that is responsible for reduced BMI.

There is some suggestion that younger onset ET might differ from older onset ET in a number of important respects. For example, a familial etiology is more common in younger-onset ET [24]. Furthermore, rate of progression differs as well, with younger onset cases seemingly progressing less rapidly [23]. Hence, we stratified ET cases based on median age of onset (50.0 years) into two groups, younger-onset vs. older-onset. Among younger onset ET cases, lower BMI was associated with longer tremor duration (i.e., the longer the disease duration, the lower the BMI).

The daily caloric intake was marginally higher in ET cases than controls, so reduction in caloric intake in ET is not a likely explanation for the observed lower BMI. Furthermore, the lack of association between BMI and tremor severity suggests that an increase in involuntary movement (i.e., tremor) is not likely to be resulting in lower BMI (through an involuntary movement-related increased burning of calories). Hence, other mechanistic possibilities are more likely, including neuroendocrine disturbances, and/or changes in basal metabolic rate. These should be explored.

Two prior studies assessed BMI in ET [13, 14], although both enrolled sample sizes that were $<1/4$ of the current sample size and only one included calorie counts on a sub-sample of 40 ET cases. Aside from tremor duration and severity, the prior studies did not assess

clinical correlates of lower BMI in ET (e.g., correlation with rest tremor, cranial tremor, etc).

Aside from postmortem and neuroimaging evidence, a number of clinical features of ET are consistent with the notion that this is a degenerative disease [5, 26, 27]; these include its association with advanced age, its progressive nature, and its association with other neurodegenerative conditions [28]. In some though not all studies, there is an olfactory deficit [29].

In summary, the lower BMI in ET we observed is consistent with the neurodegenerative hypothesis of ET. The data also suggest that some mechanism other than decreased daily caloric intake or an involuntary movement-related increased burning of calories is likely to account for this case-control difference. Additional studies are called for.

Acknowledgments

Funding: National Institutes of Health Grant R01 NS039422 and UL1 TR000040.

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Table 1
Demographic and Clinical Characteristics of ET Cases and Control Subjects

	Controls	ET Cases	Difference
Number	392	382	NA
Age in years	68.1 (11.9)	67.4 (15.3)	$t = 0.78, p = 0.77$
Female gender	218 (55.6)	196 (51.3)	$X^2 = 1.44, p = 0.23$
White race	364 (92.9)	360 (94.2)	$X^2 = 0.61, p = 0.43$
Years of education	15.4 (3.4) Median = 16.0	15.1 (3.8) Median = 16.0	$MW = 0.28, p = 0.78$
Number of rooms in Home/number of people living in home	3.3 (1.7) Median = 3.0	3.4 (1.7) Median = 3.0	$MW = 1.37, p = 0.17$
Number of live births (women)	2.1 (1.7) Median = 2.0	2.1 (1.5) Median = 2.0	$MW = 0.22, p = 0.83$
Years since last hospitalization	14.6 (19.3) Median = 6.0	14.9 (20.4) Median = 6.0	$MW = 0.29, p = 0.77$
Total tremor score	3.9 (2.9)	18.8 (7.2)	$t = 37.07, p < 0.001$
First- or second-degree relative with ET or tremor	41 (10.5)	232 (60.7)	$X^2 = 214.18, p < 0.001$
Tremor duration in years	NA	23.0 (18.8)	NA
Taking a medication to treat tremor	0	206 (53.9)	NA
Surgery (thalamotomy, DBS, other) for tremor	0	11 (2.8)	NA
CIRS score	5.4 (3.7) Median = 5.0	5.6 (3.7) Median = 5.0	$MW = 0.50, p = 0.62$
BMI (kg/m ²)	27.7 (5.6) Median = 26.7	26.7 (5.0) Median = 26.2	$MW = 2.16, p = 0.03$
Mean daily caloric intake (Kcal)	1397.8 (458.8) Median = 1341.6	1440.3 (427.6) Median = 1420.9	$MW = 2.16, p = 0.09$

Mean (standard deviation) or number (percent).

BMI = body mass index, CIRS = Cumulative Illness Rating Scale, DBS = deep brain stimulation, ET = essential tremor, MW = Mann-Whitney test, NA = Not applicable.