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Screening for and Estimating the Prevalence of Essential Tremor: A Random-Digit Dialing-Based Study in the New York Metropolitan Area

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Abstract

Background—There are nearly no published screening instruments for essential tremor (ET). This is a remarkable fact, given its high prevalence. Here, we assess the validity of a screening questionnaire and hand-drawn spirals and also estimate the prevalence of ET in a community sample.

Methods—Four hundred nineteen study subjects living in a geographically defined area in the New York metropolitan area were contacted using a random digit telephone dialing scheme. Seven tremor screening questions were administered and each subject drew 2 spirals. A movement disorders neurologist assigned ET diagnoses based on neurological examination.

Results—The spirals were a more sensitive test than the screening questions (73.7 vs. 26.3%); specificities of the 2 tests were similar (95.5 vs. 96.8%). The combination of both tests was not superior to the use of spirals alone. The positive predictive value of the spiral test was 43.8%. The crude prevalence of ET, 19 of 419 (4.53%, 95% CI 2.92–6.97), increased with age ($p = 0.049$).

Conclusions—A screening spiral was more sensitive than a screening questionnaire for ET and was moderately sensitive. Nearly one-half of subjects who screened positive had ET; therefore, when screening a population, one can expect the number of true positives and false positives to be roughly equivalent.

Keywords

Essential tremor; Epidemiology; Prevalence; Screening; Validity

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Disclosure Statement

Drs. E.D. Louis and P. Factor-Litvak have no competing interests.

Statistical Analyses: the statistical analyses were conducted by E.D. Louis

Introduction

There are virtually no published screening instruments for essential tremor (ET). This is a rather remarkable statement given the fact that ET is among the most common neurological diseases; indeed, it is the most frequently encountered cause of abnormal tremor in human populations [1–4]. This gap in knowledge leaves researchers, including epidemiologists and clinical neurologists, with the following dilemmas: How can one identify ET cases in the population? What approach should one take? What instrument should one use? What is the effectiveness of these instruments? The goal of this study was 2-fold. First, we evaluate the validity of 2 screening methods for ET, a 7-item questionnaire and hand-drawn spirals, within the context of a clinical epidemiological study that involved the enrollment of more than 400 study subjects ascertained in a geographically defined area in the New York metropolitan area using a random digit telephone dialing scheme. Second, we report the crude and age-standardized prevalence of ET in this sample, as described below.

Methods

Study and Subjects

A case–control study of the environmental epidemiology of ET was conducted between 2000 and 2009 [5, 6]. At the time of enrollment, all subjects signed written informed consent approved by the Columbia University Medical Center (CUMC) institutional ethics board. As detailed previously [5, 6], the ET cases were derived from 2 main sources: the billing records of the Center for Parkinson's Disease and Other Movement Disorders at the Neurological Institute of New York, CUMC and the membership of the International Essential Tremor Foundation who both responded to study advertisements in their newsletter and lived in the New York metropolitan region. These cases are not the subject of the present analyses.

Potential controls, who are the 419 subjects that are the focus of the current analyses, were enrolled using a random digit telephone dialing scheme; this enrollment was staggered slightly behind that of ET cases to allow for frequency-matching on age and gender. Telephone calls were made by trained staff who restricted the calls to a specific set of telephone area codes that were defined by those ET subjects who had been enrolled in the study to date. These area codes were all in the New York metropolitan area in New York, New Jersey and Connecticut. The callees were frequency-matched to ET cases based on age and gender; hence, a call would terminate if the callee did not fall within specific pre-defined age and gender strata. The 419 callees who passed this initial screening step were then administered a brief set of 7 screening questions for tremor (table 3) and, regardless of their responses, all of their names were passed on to the research team at CUMC for consent and enrollment. These 419 callees are the focus of the current analyses.

Medical History, Spiral Drawing, Videotaped Tremor Examination and Diagnostic Confirmation

After signed consent, a medical history that included questions on demographics, medications and medical illnesses was administered in person by trained testers to all the

419 study participants. A videotaped neurological examination, administered to all study participants, included assessments of postural and kinetic tremors (arms), head tremor (neck), voice tremor, and jaw tremors, as well as tremor at rest and signs of Parkinsonism and dystonia. The videotaped examination included one test for postural tremor and 5 tests for kinetic tremor (e.g., pouring, using spoon, drinking and hand-drawn spirals) performed with each arm (12 tests total). The hand-drawn spirals were drawn freely on a blank, standard 8.5 × 11-inch sheet of paper using a ballpoint pen while the participant was seated at a table. The paper was centered at right angles (horizontally) directly in front of them and held down by their other hand. Participants started at the center of the page, without lifting their pen. They were asked not to rest their writing hand, wrist or arm on the table while drawing and to produce a spiral with each hand.

A neurologist specializing in movement disorders (E.D.L.) used a reliable [7] and valid [8] clinical rating scale, the Washington Heights-Inwood Genetic Study of Essential Tremor Rating Scale, to rate postural and kinetic tremor during each test: 0 (none), 1 (mild), 1.5 (moderate amplitude and clearly oscillatory but only sometimes of moderate amplitude, 2 (moderate), 3 (severe) (see examples in Louis et al. [9]). A total tremor score (range 0–36), which is an assessment of postural and kinetic tremor in the arms during 12 tests, was assigned to each participant.

A diagnosis of normal or ET was carefully assigned (E.D.L.) to each of the 419 participants based on the in-person medical history and videotaped examination (including the hand-drawn spirals). ET required moderate or greater amplitude kinetic tremor of the arms (rating 2) during at least 3 tasks, in the absence of Parkinson's disease (PD), dystonia or another identifiable cause (e.g., medication-induced tremor) [7, 10, 11].

Definitions

For the 7-item screening questionnaire, a positive screen was a 'yes' response to one or more screening question(s). For the hand-drawn spirals, a positive screen was a rating 1.5 (i.e., tremor that was more than mild) in either the right or left spiral. We also assessed the combined use of the 2 tests, defining a positive screen as a 'yes' response to one or more screening question(s) AND/OR a rating 1.5 in either spiral. Sensitivity was the proportion of ET-diagnosed participants who screened positive, and specificity was the proportion of non-ET diagnosed participants who screened negative. Positive predictive value was the proportion of ET cases among participants who had screened positive. Negative predictive value was the proportion of non-ET cases among participants who had screened negative.

Statistical Analyses

Data were analyzed separately in SPSS (version 21.0). We compared the demographic and clinical characteristics of enrollees diagnosed with ET to those who were not diagnosed with ET (chi-square tests, Fisher's exact tests, Student's t tests). In a logistic regression analysis, we assessed the association between ET (dependent variable) and age group (<60, 60–64, 65–69, 70–74, 75–79, 80 years). We reported the crude prevalence of ET. The crude prevalence of ET was associated with age but not with gender or race; therefore, we also report a prevalence that was age-standardized to the 2010 United States population [12].

Results

The 419 enrollees ranged in age from 18 to 92 years (table 1); of these, 19 were diagnosed with ET (crude prevalence 4.53%, 95% CI 2.92–6.97; age-standardized prevalence 1.57%, 95% CI 1.57–1.57). Five enrollees were diagnosed with other movement disorders (2 PD, 2 dystonia, 1 myoclonus). The ET cases and controls were similar with respect to age, gender, race and education (all p values >0.05 ; table 1); the total tremor score was higher in ET cases than non-ET cases (table 1, Student's t test 15.47, $p < 0.001$).

The prevalence of ET increased by age group ($p = 0.049$; table 2) but did not differ by gender (8 of 173, 4.6% in men vs. 11 of 246, 4.5% in women, chi-square test 0.005, $p = 0.94$) or race (17 of 363, 4.7% in whites vs. 2 of 56, 3.6% in non-whites, Fisher's exact test, $p = 1.00$). Four (21.1%) of the 19 ET cases had previously been diagnosed with ET by a doctor; the remainder had not. One (5.3%) of the 19 ET cases took daily medication for their tremor. One (5.3%) ET case had neck tremor and 1 (5.3%) had jaw and voice tremors on examination; both of these were women.

Responses to the 7 tremor screening questions are shown (table 3). A larger proportion of ET cases than non-ET cases endorsed these questions as positive (table 3).

A spiral rating ≥ 1.5 in either arm was present in 14 (73.7%) of 19 ET cases and 18 (4.5%) of 400 non-ET cases (table 4). The combination of a positive screening question result AND/OR a positive spiral rating result was seen in 14 (73.7%) of the 19 ET cases and 30 (7.5%) of the 400 controls (table 4). Sensitivity, specificity, positive predictive value and negative predictive value of the screening questions and spirals are shown (table 4).

Discussion

There are surprisingly few published screening instruments for ET [13–16]. A study in Germany in 2008 used a 7-item screening questionnaire that was similar but not identical to ours as well as a hand-drawn spiral with one (rather than 2) hand [13]. The study used consensus criteria for ET, which are not ideal for population-based studies of ET, as the minimal number of examination tasks during which tremor must be present are not explicitly defined. Furthermore, the participants were enrolled within the framework of a genetics study. This may have resulted in self-selection of familial ET cases; such individuals are often more aware of tremor and hence more likely to screen positive for tremor. As in our study, the questionnaire had a sensitivity that was lower than that of the spiral, although neither of the sensitivity was particularly high (43.5 vs. 52.6%) [13]. We previously assessed the sensitivity of a 12-item screening questionnaire for ET in the Washington Heights-Inwood Community in New York, finding that it picked up only 32 of 87 (36.8%) ET cases; one limitation of the study was the low mean level of education of study subjects, which may have driven the sensitivity down [14]. By contrast, a door-to-door survey in Turkey [15] reported that 72 of 89 (80.9%) ET cases responded 'yes' to the question 'do you often have shaking or tremor that you cannot control'? We have previously reported the number of non-ET subjects enrolled in this study who had spiral scores ≥ 1.5 , but did not assess the

proportion of ET cases ascertained from the random digit dialing scheme who had spiral scores in this range or the responses to the 7-item screening questionnaire [16].

One of the main findings of this study is that the spirals were a more valid screening method than the screening questions, with higher sensitivity and positive predictive values. Still, the sensitivity was no greater than 73.7%. Furthermore, the combination of the 2 methods was no more valid than the use of the screening spirals alone. One obvious limitation of the screening spiral is the need to collect such spirals as well as rate them; the use of a screening questionnaire is simpler to administer and interpret.

The positive predictive value of the spirals was 43.8%, meaning that nearly one-half of those who screen positive are likely to have ET. This indicates that when screening for ET in population-based studies, one can expect the number of true positives and false positives to be roughly equivalent. When planning ET research, this is encouraging, because it means that every 2 post-screen neurological examinations are expected to yield approximately one ET case.

The most important distinction in population-based studies of tremor is between enhanced physiological tremor, which is highly prevalent, and ET. If a 'positive' screening test requires only mild tremor, one will certainly include individuals with enhanced physiological tremor among those who screen positive. If a 'positive' screening test requires tremor that is more severe, ET cases may fail to screen positive and will not be ascertained. Hence, a balance must be achieved. A more thorough evaluation of cases after the screening process, either with a detailed neurological examination as we performed or using other methods (e.g., tremor analysis) is an important step in terms of ensuring that those who screened positive have ET rather than enhanced physiological tremor.

The crude prevalence of ET in the current study was 4.53%; among those of age 60 years and older, the crude prevalence was 18 of 381 (4.72%) and in those of age 65 years and older, it was 16 of 316 (5.06%). By comparison, in population-based studies of ET in which either (1) all study participants were examined or (2) the investigators provided information on the validity of their screening questionnaire thereby allowing one to adjust the crude prevalence estimates, the prevalence (60–65 years and older) is strikingly similar (e.g., 4.1% in New Guinea [2, 17], 6.3% in Turkey [2, 18] and 7.0% in Spain [1, 2]). As in prior reports [2], the prevalence of ET in the current study increased with age and continued to rise even in the oldest age stratum [19]. The prevalence did not differ between men and women; this has been a similar finding in most studies to date [2].

The mean total tremor score in the current ET cases was 14.7, indicative of overall mild tremor. This is consistent with the additional observation that the large majority of these cases was diagnosed by the study physician and had not been diagnosed with ET previously. Similarly, only one ET case was taking daily medication for tremor. In published population-based studies, the mean total tremor score among ET cases has been similarly mild (e.g., 16.4 in northern Manhattan [16], 17.8 in Turkey [15]); by comparison, ET patients ascertained from clinic-based studies or ET brain banks tend to have higher total tremor

scores (e.g., 18.8 [16] and 24.2 [16]). The low prevalence of cranial tremors in the current sample further speaks to the mild overall nature of the tremor in our cases.

This study should be interpreted within the context of certain limitations. First, although the sample was ascertained in a geographically-defined area in the New York metropolitan area using a random-digit telephone dialing scheme, this was not a population-based door-to-door survey; indeed, the age and gender structure of the 419 enrollees was defined by that of the ET cases in the case-control study. Also, the telephones we called were land lines; such a strategy is less likely to ascertain individuals in younger age groups. Second, the sample was moderately to highly educated, and individuals of lower education might not perform as well on a screening questionnaire; however, educational level should not affect the sensitivity of the screening spirals. Third, in receiving the random digit telephone call from a stranger; respondents may have under-reported medically sensitive issues; this could have reduced the apparent sensitivity of the questionnaire. Fourth, our study subjects drew spirals under standardized conditions; it is possible that under less supervised conditions (e.g., as might exist in the field), the spirals could be less useful. For example, drawing spirals quickly can lessen the amount of observed tremor. For this reason, it is important to provide detailed instructions and supervised feedback in the field. For mailed spirals, it would be important to provide detailed written directions as well as a visual example of the desired spiral. Finally, the ability to contact individuals in the population may be regulated by state/regional laws, which could limit the ability of investigators to screen individuals. This must be kept in mind when considering the utility of screening instruments.

This study also had several strengths. Our prevalence estimate of ET is based on a detailed neurological examination, and all participants were examined regardless of their responses to screening questions. These diagnoses were assigned by a movement disorder neurologist using diagnostic criteria that are both reliable [7] and valid [11]. Second, we examined several different screening methods as well as their combination, in order to derive the optimal screening method.

In summary, a screening spiral was more sensitive than a screening questionnaire for ET, which was moderately sensitive. Nearly one-half of subjects who screened positive had ET; therefore, when screening a population, one can expect the number of true positives and false positives to be roughly equivalent.

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Table 1

Demographic and clinical characteristics of 419 enrollees

	All enrollees (n = 419)	Enrollees diagnosed with ET (n = 19)	Enrollees not diagnosed with ET (n = 400)
Age, years	69.2±9.8	71.1±14.8	69.1±9.5
Range	18–92	18–84	26–92
Female gender	246 (58.7)	11 (57.9)	235 (58.8)
White race	363 (86.6)	17 (89.5)	346 (86.5)
Education, years	15.2±3.4	15.2±3.2	15.2±3.4
Range	0–27	8–23	0–27
Total tremor score	4.3±3.8	14.7±4.4	3.8±2.9
Range	0–27	5–27	0–15

Values represent mean ± SD or number (percentage). Ranges are also specified.

Table 2

Crude prevalence of ET by age

Age group, years	Proportion with ET	Crude prevalence of ET per 100 (95% CI)
<60	1/38	2.63 (0.47–12.49)
60–64	2/65	3.08 (0.85–10.55)
65–69	4/109	3.67 (1.44–9.06)
70–74	3/97	3.09 (1.06–8.70)
75–79	3/55	5.45 (1.87–14.85)
80	6/55	10.91 (0.51–21.83)

In a logistic regression analysis, ET (dependent variable) was associated with age group ($\beta = 0.33$, $p = 0.049$).

Table 3

Four hundred nineteen enrollees' responses to 7 screening questions for tremor

	'Yes' response (all 419 enrollees)	'Yes' response (19 enrollees diagnosed with ET)	'Yes' response (400 enrollees not diagnosed with ET)
Do you often have shaking or tremor that you can not control?	10 (2.4)	4 (21.1) **	6 (1.5)
Do other people often tell you that you have a tremor?	6 (1.4)	3 (15.8) **	3 (0.8)
Has a doctor diagnosed you as having familial tremor or benign essential tremor?	7 (1.7)	4 (21.1) **	3 (0.8)
Do you often have shaking or tremor in your hands or arms that you can not control?	13 (3.1)	4 (21.1) **	9 (2.3)
Does your head often shake uncontrollably?	1 (0.2)	1 (5.3) *	0 (0.0)
Does your voice almost always shake uncontrollably?	0 (0.0)	0 (0.0)	0 (0.0)
Does your hand usually tremble when you hold a pen or write your name?	5 (1.2)	3 (15.8) **	2 (0.5)
	419 enrollees	19 ET	400 non-ET
Answered 'yes' to 1 screening question	18 (4.3)	5 (26.3) **	13 (3.3)
Answered 'yes' to 2 screening questions	12 (2.9)	5 (26.3) **	7 (1.8)
Answered 'yes' to 3 screening questions	7 (1.7)	4 (21.1) **	3 (0.8)
Answered 'yes' to 4 screening questions	4 (1.0)	3 (15.8) **	0 (0.0)
Answered 'yes' to 5 screening questions	1 (0.2)	1 (5.3)	0 (0.0)

All values number (percentage). Data for some variables were missing in <1% of participants.

*
p < 0.05 (Fisher's exact test, comparing ET to non-ET).**
p < 0.01 (Fisher's exact test, comparing ET to non-ET).

Table 4

Validity of screening questions and screening spirals

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Screening questions	5/19 (26.3)	387/400 (96.8)	5/18 (27.8)	387/401 (96.5)
Spirals	14/19 (73.7)	382/400 (95.5)	14/32 (43.8)	382/387 (98.7)
Combination of screening questions and spirals	14/19 (73.7)	370/400 (92.5)	14/44 (31.8)	370/375 (98.7)

All values are proportions (percentage).