Journal of the Neurological Sciences 393 (2018) 45–50

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Validity of probands' reports and self-reports of essential tremor: Data from a large family study in North America

Elan D. Louis[a,b,c,*], Nora Hernandez[a], Adonai A. Sebastian[a], Lorraine N. Clark[d,e], Ruth Ottman[f,g,h,i]

[a] Division of Movement Disorders, Department of Neurology, Yale School of Medicine, Yale University, New Haven, CT, USA
[b] Department of Chronic Disease Epidemiology, Yale School of Public Health, Yale University, New Haven, CT, USA
[c] Center for Neuroepidemiology and Clinical Neurological Research, Yale School of Medicine, Yale University, New Haven, CT, USA
[d] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[e] Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY, USA
[f] G.H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[g] Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[h] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA
[i] Division of Epidemiology, New York State Psychiatric Institute, New York, NY, USA

ARTICLE INFO

Keywords:
Essential tremor
Movement disorders
Epidemiology
Genetics
Validity
Family history data

ABSTRACT

The search for genes for essential tremor (ET) is active. Researchers often depend on probands' reports or self-reports to assign disease status to relatives. Yet there are surprisingly few data on the validity of these reports. In two prior studies, with small sample sizes, validity was poor (sensitivity = 16.7–43.3%). In the current study, ET probands and their relatives were screened for tremor and then underwent a videotaped in-person neurological examination. One investigator then assessed the screening questionnaires and videotapes to assign diagnoses of ET, borderline tremor or other diagnosis. There were 98 probands and 243 relatives (105 with ET, 34 with borderline tremor). Educational attainment was high (15.6 ± 2.7 years). Probands failed to report tremor in 39/139 relatives with ET or borderline tremor; conversely, they reported tremor in 32/104 relatives without ET or borderline tremor. Thus, in total, there were 71/243 (29.2%) mis-identifications. Thirty six of 139 ET and borderline ET cases failed to self-report tremor; conversely, 30/104 relatives without ET or borderline tremor self-reported tremor. Thus, in total, there were 66/243 (27.2%) mis-identifications. In summary, in individuals with greater educational attainment, the validity of reported information on ET was considerably higher than previously reported. Despite this, even among well-educated individuals in North America, probands' reports and self-reports misclassified approximately 30% (i.e., one-in-three) of relatives.

1. Introduction

In genetic and genetic epidemiological studies, investigators often must rely on family history information (i.e., informants' reports of disease in relatives) or self-reports of relatives, without accompanying neurological examinations, to assign disease status to relatives. For example, neurological examinations are difficult or impossible to obtain in relatives who live far away from investigators (e.g., in other countries), refuse an in-person evaluation, or are deceased; for these relatives, investigators must rely on family history information or self-reported symptoms or diagnoses. Thus, it is crucial to evaluate the validity of these types of reported information (henceforth referred to in this paper as "reported information").

Studies of the genetic basis for essential tremor (ET) are current and ongoing [1]; however, there is relatively little information on the validity of reported information, and the limited data available are from restricted populations. One study in New York [2, 3], and a second in Singapore [4], reported very low sensitivities. The two prior studies were limited by modest sample sizes and participants likely to have low health literacy due to lower educational attainment. There are no other data.

Here, we ascertained a large number of North American probands (n = 98) and relatives (n = 243; 105 of these with ET) to assess the validity of reported information in ET. Although not selected based on

Abbreviations: ET, essential tremor; FASET, Family Study of Essential Tremor; PD, Parkinson's disease

* Corresponding author at: Yale School of Medicine, Department of Neurology, 15 York Street, PO Box 208018, New Haven, CT 06520-8018, USA.
E-mail address: elan.louis@yale.edu (E.D. Louis).

https://doi.org/10.1016/j.jns.2018.08.006
Received 11 April 2018; Received in revised form 2 July 2018; Accepted 3 August 2018
Available online 06 August 2018
0022-510X/

educational attainment, our enrollees had higher educational attainment, which allowed us to assess validity within the context of such higher attainment. An additional aim was to evaluate whether characteristics of probands or relatives (e.g., age, educational level, gender) correlated with the validity of their respective reports. The goal of these analyses was to provide granular data to investigators engaged in the studies of the genetics, epidemiology and genetic epidemiology of ET.

2. Methods

2.1. Ascertainment of probands

ET cases (probands) and their relatives were enrolled in a study of ET, the Family Study of Essential Tremor (FASET) (Phase 2, September 2015 – present) [5], which enrolled participants throughout the United States. The study was advertised on several ET society websites. The three inclusion criteria for probands were: (1) a diagnosis of ET assigned by a doctor, (2) age of tremor onset ≤40 years (later changed to ≤50 to be more inclusive), (3) ≥2 living relatives in the United States who have ET that was diagnosed by a doctor; these relatives were not reported to have dystonia or Parkinson's disease (PD). The exclusion criterion for probands was a diagnosis of dystonia or PD. Potential ET probands contacted the study coordinator. Prior to final selection for enrollment, four Archimedes spirals (two right, two left) were submitted by probands, and rated by a senior neurologist specializing in movement disorders (E.D.L.). Probands were included if one or more of the spirals had a Washington Heights Inwood Genetic Study of Essential Tremor rating that indicated moderate or greater tremor [6].

2.2. Ascertainment of relatives

During a telephone interview with the proband, relatives were identified and reported by the proband to be affected or unaffected [5]. With the proband's permission, these relatives were then contacted by telephone, and a screening questionnaire was administered to these relatives that included four questions about tremor ("Do you have shaking or tremor that you can't control?"; "Does your hand tremble when you hold a pen?", "Does your head sometimes shake?", "Does your voice sometimes tremble?") [6].

2.3. In-person evaluation

Trained personnel traveled to the probands' and relatives' homes to conduct in-person evaluations; the evaluation included several questionnaires regarding demographic and clinical features and a videotaped neurological examination [5]. The evaluation was conducted on all available relatives regardless of whether they screened positive or negative for tremor in the interview. In addition to an assessment of cranial tremors (neck, jaw and voice), the examination included a detailed assessment of postural, kinetic, intention and rest tremors of the limbs, as well as dystonia and other movement disorders [7]. Neck tremor in ET was coded as present or absent and was distinguished from dystonic tremor by the absence of twisting or tilting movements of the neck, jerk-like or sustained neck deviation, or hypertrophy of neck muscles [8]. E.D.L. reviewed all videotaped examinations, and the severity of postural and kinetic arm tremors was rated on 12 examination items using a reliable scale [9]. As reviewed elsewhere [10, 11], ratings were 0, 0.5, 1.0, 1.5, 2, 3 and 4, and resulted in a total tremor score (range = 0–46 [maximum]) [7]. The study was approved by Columbia and Yale University Institutional Review Boards; participants signed written informed consent.

2.4. Diagnoses

All *ET diagnoses* in probands and relatives were assigned by E.D.L. based on review of questionnaires and videotaped neurological examination using published diagnostic criteria (moderate or greater amplitude kinetic tremor during three or more activities or a head tremor in the absence of PD or another known cause [e.g., medication-induced tremor, tremor from hyperthyroidism]) [5, 6, 9]. These diagnostic criteria for ET were developed for a population-based genetic study and, based on data from approximately 2000 normal (non-diseased controls), the criteria carefully specify the specific examination maneuvers during which tremor should be present and the severity of tremor that should be evident during these maneuvers to distinguish normal from ET. These criteria have been shown to be both reliable [9] and valid [12], and have been used by tremor investigators in the United States and internationally [13–22]. As in a prior study, *borderline tremor* was a diagnosis assigned to individuals who did not fully meet strict diagnostic criteria for ET (defined above) but were nonetheless considered by E.D.L. to have clinical features that aligned them more with ET than normal [23]. The diagnosis of *dystonia* was confirmed using published diagnostic criteria [24], as was the diagnosis of *PD* [25]. Some patients with ET may develop mild dystonia [26]; *ET and dystonia* was the diagnostic category used for patients with long-standing, severe ET who were developing mild dystonic movements or postures (e.g., mild torticollis).

2.5. Statistical analyses

Analyses were performed in SPSS (Version 24.0). We compared proportions using chi-square tests or Fisher's tests and continuous variables using Student's *t*-tests. We examined agreement between probands' and relatives' reports using kappa statistic.

Sensitivity of probands' reports was defined as the proportion of relatives diagnosed with ET who had been reported by the proband as having tremor. *False negatives* were relatives with ET who were not reported by the proband as having tremor. The *specificity* of the probands' reports was the proportion of relatives not diagnosed with ET whom the proband had reported as not having tremor. *False positives* were relatives without ET who were reported by the proband as having tremor.

Sensitivity of the relatives' self-reports was the proportion of relatives diagnosed with ET who had self-reported tremor (i.e., they answered "yes" to at least one of four screening questions). *False negatives* were relatives with ET who had not self-reported tremor. The *specificity* of the relatives' self-reports was the proportion of relatives not diagnosed with ET who had not self-reported tremor. *False positives* were relatives without ET who self-reported tremor.

3. Results

3.1. General

There were 125 probands and 320 relatives whose regional distribution in the United States was as follows: northeast (16.9%), southeast (27.5%), southwest (7.5%), middle west (17.4%), and west (30.7%). We excluded 27 probands whose diagnosis was not ET (19 ET and dystonia, 6 dystonia, 2 borderline tremor). We also excluded the 77 relatives of these 27 probands. The final sample comprised 98 probands and 243 relatives. Demographic and clinical characteristics are shown (Table 1). Mean education for probands and relatives combined was 15.6 ± 2.7 years; in 97.5% it was ≥12 years.

The 98 probands reported that 132 (54.3%) of 243 relatives had tremor and 111 (45.7%) of 243 relatives did not have tremor (Fig. 1).

Among 132 relatives whom the proband reported as having tremor, 120 (90.9%) self-reported tremor and the remaining 12 (9.1%) did not (Fig. 1). By contrast, among 111 relatives whom the proband reported as not having tremor, 13 (11.7%) self-reported tremor and 98 (88.3%) did not (kappa = 0.79 [substantial agreement between probands' and self-reports], chi-square = 152.6, $p < .001$) (Fig. 1).

Final diagnoses among the 243 relatives were: 105 (43.2%) ET, 34