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Prevalence and Correlates of Rest Tremor in Essential Tremor: Cross-Sectional Survey of 831 Patients Across Four Distinct Cohorts

Elan D. Louis, MD MSc[1,2,3,4], **Nora Hernandez, MD**[1], and **Monika Michalec, MPH**[1]

[1]GH Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[2]Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[3]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

[4]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA

Abstract

Background—Essential tremor (ET) is among the most commonly encountered neurological disorders. Its hallmark feature is kinetic tremor. However, other tremors may also occur in ET patients, creating considerable diagnostic confusion among treating physicians. Hence, characterizing the prevalence and clinical accompaniments of these other tremors is of value. Surprisingly, there are few data on the prevalence of rest tremor in ET patients, and even fewer data on the clinical correlates of such tremor.

Methods—831 patients in four distinct settings (population, genetics study, study of environmental epidemiology, brain bank) underwent a detailed videotaped neurological examination that was reviewed by a senior movement disorders neurologist. Rest tremor was evaluated in several positions (seated, standing, lying down).

Results—The prevalence of rest tremor while seated or standing was lowest in the population-based setting (1.9%), highest in the brain bank study (46.4%), and intermediate in the remaining two settings (9.6% and 14.7%, respectively). Rest tremor was restricted to the arms and was not observed in the legs. Rest tremor was associated with older age, longer disease duration (in some studies), greater tremor severity and, to some extent, the presence of cranial tremors.

Conclusions—Rest tremor can be a common clinical feature of ET. Its prevalence is highly dependent on the setting in which patients are evaluated, ranging from as low as 1% to nearly

Correspondence: Elan Louis, Unit 198, Neurological Institute, 710 West 168th Street, New York, NY, 10032, USA. Tel: (212) 305-9194, FAX: (212) 305-1304, EDL2@columbia.edu.

Disclosure of Conflict of Interests

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

50%. Rest tremor seems to emerge as a clinical feature with advancing disease. The anatomical substrates for this type of tremor remain unknown at present.

Keywords

essential tremor; clinical; epidemiology; rest tremor; examination

Introduction

Essential tremor (ET) is one of the most commonly encountered neurological disorders [1,2]. The hallmark feature of the disease is kinetic tremor and, to a lesser degree, postural tremor [3]. Other tremors may also occur in these patients, and may serve as a source of considerable diagnostic confusion for treating physicians. Hence, study of the prevalence and clinical accompaniments of these tremors is important. One of tremors that may occur in patients with ET is rest tremor [4,5]. Yet there are surprisingly few data on the prevalence of rest tremor in this disease and even fewer data on the clinical features that accompany such tremor [4]. The aims of this study were (1) to estimate the prevalence of rest tremor in patients with ET and (2) to assess the clinical correlates of that tremor. In order to broadly address these aims across a wide range of patient settings, these analyses utilized four distinct patient samples: a population-based study in northern Manhattan [6], a genetics study [7], a study of the environmental epidemiology of ET [8], and a brain repository [9]; in total, more than 800 ET patients were studied in these four parallel datasets. Our *a priori* hypothesis was that the prevalence of rest tremor would co-vary with the severity of disease, and that its prevalence would be greatest in cohorts that were more weighted towards ET cases with severe and long-standing disease.

Methods

Four ET case samples were utilized, in whom data were collected prospectively. All cases signed written informed consent approved by our institutional ethics board.

Population-based study in northern Manhattan

The Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) was a family study of ET in the Washington Heights-Inwood community in northern Manhattan, New York. Enrollment began in 1995 and ended in 2000. There were 106 ET cases, which included 59 probands with ET, 33 of their relatives with ET, and 14 affected relatives of control probands. The design of this population-based study has been described in detail [6,10]. Each enrollee underwent a demographic and medical history and a videotaped tremor examination, as described below.

Family Study of Essential Tremor

The Family Study of Essential Tremor (FASET) was a genetics study of ET at Columbia University Medical Center (CUMC) (2011–2014). Enrollees included ET cases (probands) and their first-and second-degree relatives [7]. The study was advertised on two ET society websites. Based upon a telephone interview with the proband, relatives with ET were identified. The final sample included 207 individuals (52 probands and 155 relatives) of

whom 160 had ET. Each enrollee underwent a demographic and medical history and a videotaped tremor examination, as described below.

Study of the environmental epidemiology of ET

ET cases were enrolled in a study of the environmental epidemiology of ET, from 2000 – 2009 [8]. As described, cases were derived from two main sources: the Neurological Institute of New York at CUMC and the membership of the International Essential Tremor Foundation (IETF). After enrollment, the 388 ET cases underwent a demographic and medical history and a videotaped tremor examination, as described below.

Essential Tremor Centralized Brain Repository

The Essential Tremor Centralized Brain Repository (ETCBR) at Columbia University is a centralized repository for the prospective collection and study of ET brains [9] (2003 – 2014). ET cases were recruited as future brain donors through the IETF and other sources. Once enrolled, cases underwent a demographic and medical history and a videotaped tremor examination, as described below. These ET cases were highly selected because many were ascertained through a disease-specific organization and because they self-referred to the brain repository as future brain donors [9]. The large majority of these cases have also seen physicians who have diagnosed them with ET [11].

Medical history, videotaped tremor examination and diagnostic confirmation

In each of the four studies, the medical history included questions on demographics, medications, and features of tremor. The videotaped tremor examination included assessments of postural and kinetic tremors in the arms, as well as head (neck), voice, and jaw tremors. 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). During the enrollment phase of each study, the same senior neurologist specializing in movement disorders (E.D.L.) used a reliable [12] and valid [13] clinical rating scale, the WHIGET Tremor Rating Scale, to rate postural and kinetic tremor during each test: 0 (none), 1 (mild), 2 (moderate), 3 (severe). These ratings were summed to produce a total tremor score (range = 0 – 36), which was an assessment of postural and kinetic tremor in the arms [8]. In addition, the mean postural tremor score was the mean rating of postural tremor in the right and left arms, and the mean kinetic tremor score was the mean rating of kinetic tremor in the right and left arms. The presence of intention tremor in either arm was also noted on the finger-nose-finger movement.

The motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS)[14] was also videotaped, and this included assessments of facial expression and blink frequency; speech; rapid alternating movements; rising from a chair; standing with arms at sides; and posture, gait and arm swing. Rest tremor evaluated (1) while seated with arms fully supported by the patient's legs, (2) while standing with arms at rest by the patient's side and then while walking (these were rated together and for simplicity, this is referred to as "standing" in the remainder of the paper), and (3) while lying down (only in the ETCBR). Rest tremor was rated as present or absent in each arm and leg; it was assessed conservatively, and was not coded as present if the limb did not seem to be fully at rest (i.e., the limb had to be fully

supported while seated and lying, hanging loosely while standing, or swinging freely while walking). If rest tremor was present, laterality was commented on (i.e., more severe on one side than the other). In addition to the presence or absence of dystonic postures during sustained arm extension, the videotape was assessed for the presence of spasmodic torticollis (while seated, while walking and while lying down), voice tremor and voice breaks (during spontaneous speech, reading, sustained vowel sounds) and blepharospasm. Dystonic head tremor was carefully distinguished from ET-related head tremor by the presence of directional or irregular tremor and the tendency for the tremor to continue while the patient was supine. Voice tremor was attributed to dystonia if there were voice breaks or strangled or breathy speech. Limb tremor was attributed to dystonia when it either had an irregular (i.e., non-rhythmic) quality, a directionality (i.e., it did not rotate around a central axis), or was accompanied by dystonic postures.

In each study, the diagnosis of ET was carefully re-assessed (E.D.L) based on the history and videotaped examination. All of the cases included in these analyses met published research criteria for ET (moderate or greater amplitude kinetic tremor of the arms during at least three tasks or head tremor, in the absence of Parkinson's disease, dystonia or another neurological disorder, or another cause)[10].

Statistical analyses

Data on each of the four case samples were analyzed separately in SPSS (Version 21) using chi-square (X^2) and t tests. We examined the clinical correlates of rest tremor in three of four studies. In these analyses, we also corrected for multiple comparisons by performing a Bonferroni correction.

Results

The demographic and clinical features of ET cases are presented (Table 1). None of the cases had Parkinson's disease and none had dystonia on examination. In other words, when rest tremor was present, it was not accompanied by any other features of parkinsonism. As would be expected, the severity of arm tremor (total tremor score), the duration of tremor, and the prevalence of head tremor on examination were lowest in the population-based study and highest in the ETCBR (Table 1).

The prevalence of rest tremor was a function of the sampled cohort, with that in the population being lowest and that in the highly-selected brain donors being the highest (Table 1). Rest tremor occurred in one or more arms either while seated or standing in 1.9% of WHIGET cases, 9.6% of FASET cases, 14.7% of cases in the study of the environmental epidemiology of ET and 46.4% of cases in the ETCBR. In three of four studies, tremor while seated was more prevalent than tremor while standing (Table 1). No patients exhibited tremor in the legs or feet.

We examined the clinical correlates of rest tremor in three of four studies; in the fourth study, WHIGET, there were only two cases with rest tremor, so these analyses were not feasible. In each of the three studies, cases with rest tremor were significantly older than their counterparts without rest tremor (Table 2). In addition, cases with rest tremor had

higher total tremor scores than those without rest tremor (Table 2). In each study, cases with rest tremor had tremor of longer duration than those without rest tremor, although the difference only reached significance in one of the studies (Table 2). To a variable degree, cases with rest tremor were more likely to have voice or head tremors than were those without rest tremor (Table 2). There were no other systematic differences.

For the study of environmental epidemiology, in 6 (54.5%) of 11 cases with asymmetric rest tremor (i.e., worse in one arm both while seated and while standing), the arm with greater rest tremor also had greater action tremor; in 2 (18.2%), the arm with greater rest tremor was contralateral to the arm with greater action tremor, and in the remainder, rest tremor was symmetric. In the ETCBR, in 11 (45.8%) of 24 cases with asymmetric rest tremor, the arm with greater rest tremor also had greater action tremor; in 9 (37.5%), the arm with greater rest tremor was contralateral to the arm with greater action tremor. and in the remainder, rest tremor was symmetric. In FASET, 1 case had asymmetric rest tremor; in this case, the arm with greater rest tremor also had greater action tremor. In WHIGET, neither (0.0%) of 2 cases with rest tremor had an asymmetric rest tremor.

Discussion

The prevalence of rest tremor in ET was very much dependent on the setting in which patients were evaluated as well as the maneuver used to evaluate the tremor (e.g., population-based, non-population-based [e.g., clinical study], highly-self selected). In a population-based setting, the prevalence of rest tremor while seated or standing was only 1.9% whereas in a sample of brain donors, the prevalence of rest tremor reached nearly 50%.

Tremor was more readily visible while seated than while standing and, at least in one study, was even less prevalent while lying down. There are several possible explanations. First, tremors are highly dependent upon posture. For example, a study of patients who maintained postures requiring different angles of forward flexion in the sagittal plane, of horizontal flexion, and of elbow extension, demonstrated marked differences in tremor amplitude in these various postures [15]. Such may be the case with rest tremors as well. Second, it is possible that the limb is not as fully at rest (esp. the proximal limb) in the seated position as in the lying position.

Rest tremor was restricted to the arms and was not observed in the legs/feet. This is a contrasting point with the rest tremor of Parkinson’s disease, which may be found in the arms or the legs. The reason for this somatotopic distinction is not clear, but its diagnostic significance should not be overlooked.

A number of clinical correlates were observed, including older age, longer disease duration in some studies, greater tremor severity, and to some extent the presence of cranial tremors. In accordance with our *a priori* hypothesis, these data paint the picture of a tremor that emerges as the disease advances, and is more often a feature of severe, advanced disease rather than early, mild disease. This observation could also be of some potential diagnostic value.

The mechanisms that underlie the increasing prevalence of rest tremor in advancing disease are unclear. A study in monkeys showed that bilateral electrolytic lesions in the cerebellar dentate and interpositus nuclei resulted in tremor at rest [17]. The Vim thalamic nucleus, targeted in the surgical treatment of ET, receives cerebellar afferents but none from the basal ganglia, and this surgery results in improvements in rest tremor in ET [18]. Hence, it is possible that rest tremor has some basis in cerebellar pathology. Degenerative changes have been observed in the ET cerebellum [11] and it is likely that these increase with increasing disease duration, possibly resulting in rest tremor.

Of additional interest was that the laterality of the rest tremor did not necessarily match that of the kinetic tremor. Thus, the side with more severe rest tremor was not necessarily the side with more severe kinetic tremor. The physiological explanation is not clear, but this suggests different generators for each tremor type.

The significance of rest tremor in ET patients is unclear but is likely to be heterogeneous. We have shown previously that the presence of isolated rest tremor (i.e., in the absence of other features of parkinsonism) in advanced ET is not an indicator of the presence or emergence of Lewy body pathology in these cases [16]. Nonetheless, the emergence of rest tremor in some cases, particularly if accompanied by bradykinesia or rigidity, may be an early manifestation of emerging Lewy body disease.

There are few studies of the actual prevalence of rest tremor in patients with ET, so it is challenging to place these data in context. In a study of 64 ET cases ascertained from a tertiary referral center, 12 (18.8%) had rest tremor [4]. We are aware of no other prior prevalence estimates. The prevalence of rest tremor in the community-dwelling elderly without Parkinson's disease is difficult to quantify with certainty, although one study of 1,339 persons aged 65 and older reported that 0.6% of such individuals had UPDRS rest tremor scores that were ≥2 [19]. However, a limitation of that study was that tremor was assessed by general neurologists rather than movement disorder neurologists, and it is possible that rest tremor was over-identified [19].

This study was not without limitations. First, the tremor in these patients was examined clinically. This was not a physiological study of the tremor phenomenology. Such studies have been conducted previously [4, 20] and were not the purpose of this report, which had other *a priori* aims. Second, rest tremor was assessed while supine in only one of these studies; the prevalence during this position was lower than that observed during other positions.

In summary, rest tremor occurs in ET patients, with the prevalence very much dependent on the setting in which patients are seen and the maneuver used to evaluate the tremor, with a prevalence ranging from as low as 1% to nearly 50%. Rest tremor seems to emerge as a clinical feature of advancing disease. The anatomical substrates for this type of tremor are unknown at present.

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Table 1

Demographic and clinical features of 831 ET cases in four ET case samples

	Population-Based Study in Northern Manhattan (WHIGET)	Family Study of Essential Tremor (FASET)	Study of the Environmental Epidemiology of ET	Essential Tremor Centralized Brain Repository (ETCBR)
Sample size	106	160	388	177
Age in years	69.8 ± 18.4	60.0 ± 18.0	67.4 ± 15.3	83.7 ± 5.8
Female gender	63 (59.4)	82 (51.3)	201 (51.8)	108 (61.0)
Education in years	Not available	16.4 ± 3.5	15.1 ± 3.8	14.9 ± 3.2
Total tremor score	16.4 ± 6.7	20.1 ± 5.2	18.8 ± 7.2	24.2 ± 6.7
Tremor duration in years	15.4 ± 18.8	32.8 ± 19.3	22.8 ± 18.7	41.3 ± 22.3
Age of tremor onset in years	56.7 ± 25.6	27.0 ± 17.8	44.7 ± 22.5	42.4 ± 22.9
Currently taking medication for tremor	5 (4.7)	79 (49.4)	209 (53.9)	115 (65.0)
Surgery for essential tremor	0 (0.0)	5 (3.1)	11 (2.8)	3 (1.7)
Family history of essential tremor	106 (100)	160 (100)	119 (30.7)	48 (27.1)
Family history of Parkinson's disease	NA	NA	37 (9.5)	16 (9.0)
Voice tremor on examination	16 (15.1)	26 (16.3)	118 (30.4)	71 (40.1)
Head tremor on examination	19 (17.9)	60 (37.5)	143 (36.9)	92 (52.0)
Jaw tremor on examination	8 (7.5)	27 (16.9)	43 (11.1)	73 (41.2)
Moderate or greater tremor in one or both arms during spiral drawing	74 (69.8)	98 (61.3)	197 (50.8)	159 (89.8)
Mean postural tremor score	0.9 ± 0.8	1.0 ± 0.6	0.9 ± 0.7	1.5 ± 0.8
Mean kinetic tremor score	1.5 ± 0.6	1.8 ± 0.4	1.7 ± 0.7	2.2 ± 0.6
Intention tremor in either arm	NA	62 (38.8)	NA	137 (77.4)
Rest tremor[1] while seated while standing[2] while either seated or standing[2] while both seated and standing[2] while lying down	1 (0.9) 1/105 (1.0) 2/105 (1.9) 0/105 (0.0) NA	13 (8.1) 5/157 (3.2) 15/157 (9.6) 2/157 (1.3) NA	49 (12.6) 29/380 (7.6) 56/380 (14.7) 20/380 (5.3) NA	60/173 (34.7) 56/167 (33.5) 77/166 (46.4) 36/166 (21.7) 21/161 (13.0)

All values are means ± standard deviations or proportions (percentages).

[1] In one or both arms.

[2] Could not assess in some patients because they were unable to perform the task.

NA = not assessed.

Table 2

Association between rest tremor and demographic and clinical variables

	Family Study of Essential Tremor (FASET)	Study of Environmental Epidemiology of ET	Essential Tremor Centralized Brain Repository (ETCBR)
Age RT+ RT−	72.1 ± 13.1 58.2 ± 17.7 t = 2.94, p =0.004[1]	74.3 ± 12.0 65.9 ± 15.5 t = 4.46, p <0.001[1]	85.0 ± 5.7 82.4 ± 5.6 t = 2.92, p = 0.004[1]
Percent women RT+ RT−	11 (73.3) 69 (48.6) X^2 = 3.32, p=0.068	27 (48.2) 170 (52.5) X^2 = 0.35, p = 0.56	51 (66,2) 50 (56.2) X^2 = 1.75, p = 0.19
Total tremor score RT+ RT−	24.7 ± 6.8 19.7 ± 4.8 t = 3.66, p <0.001[1]	26.8 ± 7.7 22.4 ± 6.0 t = 4.06, p <0.001[1]	26.8 ± 7.7 22.4 ± 6.0 t = 4.06, p <0.001[1]
Tremor duration RT+ RT−	34.2 ± 19.8 32.3 ± 18.8 t = 0.38, p = 0.71	28.6 ± 22.0 21.9 ± 17.8 t = 2.54, p = 0.015	41.1 ± 21.8 39.9 ± 22.0 t = 0.34, p = 0.73
Family history of ET RT+ RT−	Not applicable (100% of cases had a family history of ET)	18 (32.1) 98 (30.2) X^2 = 0.08, p = 0.78	20 (26.0) 25 (28.1) X^2 = 0.09, p = 0.76
Family history of Parkinson's disease RT+ RT−	NA	6 (10.7) RT−30 (9.3) RT−X^2 = 0.12, p = 0.73	6 (7.8) RT−9 (10.1) RT−X^2 = 0.27, p = 0.60
Percent taking ET medication RT+ RT−	10 (66.7) 69 (48.6) X^2 = 1.77, p = 0.18	29 (51.8) 178 (54.9) X^2 = 0.19, p = 0.66	51 (66.2) 58 (65.2) X^2 = 0.02, p = 0.89
Percent with voice tremor on examination RT+ RT−	8 (53.3) 17 (12.0) X^2 = 17.34, p <0.001[1]	23 (41.8) 92 (28.5) X^2 = 3.95, p = 0.047	35 (45.5) 34 (38.2) X^2 = 0.89, p = 0.34
Percent with head tremor on examination RT+ RT−	9 (60.0) 51 (35.9) X^2 = 3.33, p = 0.068	27 (48.2) 115 (35.5) X^2 = 3.42, p = 0.18	44 (57.1) 44 (49.4) X^2 = 0.98, p = 0.32
Percent with jaw tremor on examination RT+ RT−	8 (50.0) 19 (13.2) X^2 = 13.91, p<0.001[1]	14 (25.0) 27 (8.3) X^2=13.78, p <0.001[1]	40 (54.1) 33 (34.4) X^2 = 6.61, p = 0.01

All values are means ± standard deviations or proportions (percentages). RT+ = rest tremor present in either arm while seated or standing. RT− = rest tremor not present while seated or standing. NA = not assessed.

[1] After Bonferroni correction, p < 0.05.