PAPER

Essential tremor: predictors of disease progression in a clinical cohort

J D Putzke, N R Whaley, Y Baba, Z K Wszolek, R J Uitti

J Neurol Neurosurg Psychiatry 2006;**77**:1235–1237. doi: 10.1136/jnnp.2006.086579

See end of article for authors' affiliations

Correspondence to: R J Uitti, Department of Neurology, Cannaday Bldg E-2, Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224, USA; Uitti.ryan@mayo.edu

Accepted 9 July 2006
Published Online First 25 July 2006

Objectives: To examine the utility of baseline factors to predict disease progression among a clinical cohort of patients diagnosed with essential tremor.
Measures: Tremor Rating Scale (TRS).
Methods: A clinical series of 128 consecutive patients diagnosed with essential tremor was included for study. 45 (35%) patients had at least one follow-up exam (mean = 3.6 years). Baseline predictive factors examined included age, age at onset of symptoms, disease duration, sex, handedness, total tremor rating score, asymmetric tremor ratings, location of initial tremor onset, use of drugs for movement disorders, ETOH responsiveness of tremor, association of head or neck tremor, history of depression, familial history of essential tremor, Parkinson's disease, Alzheimer's disease and other movement disorders.
Results: On average, the TRS total score increased by <1 point per year before the first visit to the clinic and by about 2 points per year during the observed study period. The increase of 2 points per year during the observed study period represented an approximate 12% annual change from the mean TRS total score at the first clinic visit. Significant ($p<0.05$) predictive factors associated with increased tremor severity at the initial clinic visit included older age, longer disease duration, use of movement disorder drugs and the presence of voice tremor (r = 0.24, 0.27, 0.25, 0.19). The major factors associated with an increase in tremor severity from the initial clinic visit to the last follow up included asymmetrical tremor ratings, unilateral initial tremor onset and longer follow-up duration (r = 0.32, 0.31, 0.30). Multivariate regression analysis accounted for about 17–30% of the variance in tremor ratings ($p<0.05$).
Conclusion: Essential tremor is a slow, progressive disease. The rate of disease progression and the factors associated with disease progression may vary throughout the disease course.

Classically, essential tremor has been described as an action tremor (postural or kinetic)—that is, bilateral and midline, affecting the arms, head or voice with occasional involvement of the legs, chin and trunk. It is often accompanied by a family history of a similar tremor. Despite the progressive nature of the disease[1] and a high prevalence rate (about 3–6% of those over 40 years of age),[2 3] there are few prospective studies on essential tremor.[4–6] In brief, tremor amplitude tends to increase and progress more medially over time (7% per year)[4 5] and a larger proportion of women have head tremor throughout the disease course[6]; functional disability and psychological distress (71% and 43% of the sample) are common.[5] The prognostic factors associated with disease progression have not been examined.

METHODS

Patients and procedures

A clinical series of 128 consecutive patients diagnosed with essential tremor by one physician (RJU) at the Mayo Clinic, Jacksonville, Florida, USA, between July 1994 and March 2000 were selected if it was at least ⩾5 years since their initial clinic visit as of March 2005. A diagnosis of essential tremor is made if patients have postural or kinetic tremor of the head, arms or legs that is not attributable to drugs, caffeine or neurological illness.

As part of routine clinical care, all patients are offered follow-up evaluations for management of essential tremor. A total of 46 (36%) patients had at least one follow-up exam (M = 3.6 years, range = 0.3–10 years). One patients was excluded due to placement of a deep brain stimulator, leaving a total of 45 patients.

The data collection procedures have been described in detail previously.[7] In short, patients were assessed at each clinic visit. The baseline and last follow-up characteristics were examined in the current study. The assessment battery included physician ratings of clinical signs, and independent living and occupational capacity, and also a record of drug use, side effects, tremor responsiveness to ETOH, initial most prominent symptom, location of the initial most prominent symptom, and current most prominent symptom and its location. The Tremor Rating Scale (TRS)[8] is a commonly used rating scale of tremor and activities of daily living. Patients were classified as having asymmetrical disease or not using four items on the TRS, two items for the right upper and lower extremity tremor ratings and two corresponding items for the left side. A difference of ⩾1 points between the total right-sided and left-sided items was considered positive for asymmetrical disease.

Statistical approach

The primary dependent measures used for the two regression analyses were (1) the total TRS score at the first clinic visit and (2) change in the TRS total score between the first clinic visit and the last follow-up examination (ie, follow TRS−baseline TRS). Regression analyses consisted of two steps.[9 10] Firstly, bivariate correlation analyses (ie, point biserial correlations between binary and continuous variables) were performed between the dependent measure and each predictor variable. Predictor variables with a p value of ⩽0.15 were then entered into a multivariable regression analysis using the ''Enter'' method. The predictor variables included age, sex (male = 0, female = 1), handedness (right = 0, left = 1 (ambidextrous not included, n = 2)), age at onset of symptoms, disease duration, baseline TRS total

Abbreviation: TRS, Tremor Rating Scale.

score (predictor for change score only), asymmetrical tremor ratings (bilateral = 0, asymmetrical = 1), number of days between the baseline and last follow-up visit (predictor for change score only), use of drugs for movement disorder (no = 0, yes = 1), tremor ETOH responsive (no = 0, yes = 1), presence of head or neck tremor (no = 0, yes = 1), presence of voice tremor (no = 0, yes = 1), self-reported tremor onset (bilateral = 0, unilateral upper extremity or head/neck = 1), and several medical history indicators, including history of depression and family history of any neurodegenerative disorder or motor neurone disease or specific history of essential tremor, Parkinson's disease, Alzheimer's disease or amyotrophic lateral sclerosis (with each history variable coded as not present = 0, present = 1). Most patients (82%) had not taken drugs for tremor 8 or more hours before the clinical evaluation. Results were re-run excluding these patients, and similar results emerged.

RESULTS

In general, the overall essential tremor sample was equally represented by men (53%) and women (47%), were predominantly right-handed (91%), had a mean age of onset of symptoms of 52 years, and had a mean age of 71 years at the time of the first clinic visit (table 1). About 14% reported a positive history of depression and 61% a family history of a neurodegenerative disorder or motor neurone disease. About one third (34%) reported using drugs for tremor at the time of the first clinic visit. In all, 47% (about half) of the sample reported bilateral initial tremor onset and 55% (about half) presented with asymmetrical disease. Those with a follow-up evaluation had a considerably greater tremor rating score at the first clinic visit (mean TRS score of 19 *v* 15), a higher proportion of patients with head or neck affected (67% *v* 47%), and a higher proportion with bilateral upper extremity self-reported tremor onset (62% *v* 39%).

On using the self-reported disease onset date to determine disease duration, the average annualised change in TRS at the first clinic visit (the mean TRS score at baseline divided by the mean disease duration in years) was a little less than 1 point per year (0.88; 0.82 when considering only those with follow-up). The annualised change on the TRS over the follow-up study period (mean TRS change score divided by the mean follow-up duration, (ie, 7.98/3.6 years)) was about 2.2 points per year, or about 12% of the mean TRS score (ie, 19) at baseline.

Four factors were significantly ($p<0.05$) related to increased tremor ratings at baseline, including (1) older age at first clinic visit ($r = 0.24$), (2) longer disease duration ($r = 0.27$), (3) use of drugs for movement disorder ($r = 0.25$) and (4) the presence of voice tremor ($r = 0.19$). Two other predictor variables met the $p<0.15$ criterion for inclusion in multivariate analyses—that is, asymmetrical tremor ratings and a positive family history of essential tremor were associated with increased tremor ratings over time. Results of the regression analysis (table 1) showed that increased tremor ratings were associated with (1) an increased age at the first clinic visit and (2) longer disease duration.

Three factors were significantly ($p<0.05$) related to increased tremor ratings from baseline to last follow-up, including a unilateral or head or neck self-reported location of tremor onset ($r = 0.32$), asymmetrical disease ($r = 0.31$) and longer duration between baseline and last follow-up ($r = 0.30$). Two other predictor variables met the $p<0.15$ criteria for inclusion in multivariate analyses—that is, shorter disease duration at baseline and a negative family history of Parkinson's disease were associated with increased tremor ratings over time. Results of the regression analysis (table 1) showed that none of the individual predictor variables emerged as significant ($p>0.05$).

Table 1 Demographic characteristics

	Overall sample	Those with follow-up	Those without follow-up
Age at first clinic visit (years)	71 (10.3)	72 (10.1)	71 (10.4)
Age at onset of symptoms (years)	52 (20.2)	49 (21.0)	54 (19.8)
Disease duration (years)	19 (18.7)	23 (18.6)	17 (18.5)
Tremor Rating Scale (baseline)*	16 (10.3)	19 (10.3)	15 (10.0)
	n (%)	**n (%)**	**n (%)**
Sex			
Female	60 (47)	23 (51)	37 (45)
Male	68 (53)	22 (49)	46 (55)
Handedness			
Right	117 (91)	42 (94)	75 (91)
Left	7 (6)	1 (2)	6 (7)
Ambidextrous	4 (3)	2 (4)	2 (2)
Use of drugs for movement disorder			
No	77 (60)	25 (56)	52 (63)
Yes	44 (34)	17 (38)	27 (32)
Missing	7 (6)	3 (6)	4 (5)
Tremor ETOH responsive			
No	36 (28)	12 (27)	24 (29)
Yes	58 (45)	23 (51)	35 (42)
Unknown	34 (27)	10 (22)	24 (29)
Head or neck tremor involvement*			
No	59 (46)	15 (33)	44 (53)
Yes	69 (54)	30 (67)	39 (47)
Voice tremor			
No	56 (44)	17 (38)	39 (47)
Yes	72 (56)	28 (62)	44 (53)
Asymmetrical tremor ratings			
No	57 (45)	25 (56)	32 (39)
Yes	71 (55)	20 (44)	51 (61)
Self-reported tremor onset*			
Bilateral UE	60 (47)	28 (62)	32 (39)
Unilateral UE or head/neck	68 (53)	17 (38)	51 (61)
History of depression			
No	110 (86)	35 (78)	75 (90)
Yes	18 (14)	10 (22)	8 (10)
Family history of MD or NDD			
No	53 (41)	15 (33)	38 (46)
Yes	75 (59)	30 (67)	45 (54)
Family history of ET			
No	88 (69)	29 (64)	59 (71)
Yes	40 (31)	16 (36)	24 (29)
Family history of Parkinson's disease			
No	120 (94)	42 (93)	78 (94)
Yes	8 (6)	3 (7)	5 (6)
Family history of Alzheimer's disease			
No	124 (97)	43 (96)	81 (98)
Yes	4 (3)	2 (4)	2 (2)

ET, essential tremor; MD, movement disorder; NDD, neurodegenerative disorder; UE, upper extremities.
Values are expressed as mean (SD).
*$p<0.05$.

DISCUSSION

On average, the TRS total score increased by <1 point per year before the first clinic visit and by about 2 points per year during the observed study period. The 2 points per year increase during the observed study period represented an approximate 12% annual change from the mean TRS score at the first clinic visit. Predictive factors associated with disease progression during the ''preclinical'' (ie, up to the first clinic visit) and ''clinical'' phase were different, although duration

Table 2 Regression analyses

	Standardised β coefficient	p Value
Multivariate predictors of overall tremor at the first clinic visit		
Overall model, $R^2 = 0.17$, $p<0.001$		
Age at first clinic visit (years)	0.185	0.037
Disease duration (months)	0.198	0.029
Current use of drugs for movement disorder	0.142	0.125
Voice tremor	0.132	0.128
Asymmetric tremor ratings	0.049	0.583
Family history of essential tremor	0.096	0.288
Multivariate predictors of tremor change scores		
Overall model, $R^2 = 0.31$, $p<0.05$		
Disease duration (months)	−0.072	0.626
Tremor rating score (baseline)	−0.176	0.255
Length of follow-up evaluation	0.242	0.118
Asymmetrical tremor ratings	0.297	0.062
Self-reported tremor onset location	0.127	0.416
Family history of Parkinson's disease	−0.139	0.339

All variables entered into the model using the ''Enter'' method. ETOH history was not included owing to the large number of unknown values (n = 34, 27%). ETOH history was not significantly related to overall tremor severity in the multivariable model when including only those with valid ETOH values (p = 0.59).

with disease was common to both. During the preclinical period, the most important factors associated with increased tremor severity included older age, longer disease duration, use of drugs for movement disorder and the presence of voice tremor.

The most important factors associated with disease progression during the observed follow-up period were two variables that capture the degree of asymmetrical disease—that is, both asymmetrical self-reported tremor onset and asymmetrical tremor ratings at the first clinic visit were associated with an increased rate of tremor severity over time. In general, small to moderate asymmetry is common in essential tremor, with increased tremor severity more common on the non-dominant side.[11] In the current sample, about 55% (about half) of the sample presented with asymmetrical disease and 47% (about half) reported an asymmetrical tremor onset. In contrast with previous reports,[11] increased tremor rating severity was more common on the dominant side (52 of 71, 73%). Patients may be more likely to seek treatment when tremor-related functional limitations affect the dominant side. This may partly explain the differences between the current clinical sample and the previously reported community-based sample. As with Parkinson's disease,[12] asymmetrical disease may be associated with a different rate of disease progression in essential tremor.

Note that some of the predictive factors examined were based on patients' self-reports, which have been shown to be biased in some cases.[13] Future epidemiological studies using stratified sampling methods will help confirm the reported findings in this clinic-based cohort.

ACKNOWLEDGEMENTS

This study was supported, in part, by the Smith Fellowship given to John Putzke, PhD, Yasuhiko Baba, MD, Nathaniel R Whaley, MD, and the Morris K Udall NIH Parkinson's Disease Center of Excellence Grant at Mayo Clinic, Jacksonville, Florida, USA.

Authors' affiliations
J D Putzke, N R Whaley, Y Baba, Z K Wszolek, R J Uitti, Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA

Competing interests: None declared.

REFERENCES

1 **Louis**, ed. Essential tremor. *Lancet Neurol* 2005;**4**:100–10.
2 **Dogu O**, Sevim S, Camdeviren H, *et al*. Prevalence of essential tremor: door-to-door neurologic exams in Mersin Province, Turkey. *Neurology* 2003;**61**:1804–6.
3 **Rautakorpi I**, Takala J, Marttila RJ, *et al*. Essential tremor in a Finnish population. *Acta Neurol Scand* 1982;**66**:58–67.
4 **Elble RJ**. Essential tremor frequency decreases with time. *Neurology* 2000;**55**:1547–51.
5 **Rajput A**, Robinson CA, Rajput AH. Essential tremor course and disability: a clinicopathologic study of 20 cases. *Neurology* 2004;**62**:932–6.
6 **Hardesty DE**, Maraganore DM, Matsumoto JY, *et al*. Increased risk of head tremor in women with essential tremor: longitudinal data from the Rochester Epidemiology Project [see comment]. *Mov Disord* 2004;**19**:529–33.
7 **Uitti RJ**, Baba Y, Wszolek ZK, *et al*. Defining the Parkinson's disease phenotype: initial symptoms and baseline characteristics in a clinical cohort. *Park Relat Disord* 2005;**11**:139–45.
8 **Fahn S**, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, eds. *Parkinson's disease and movement disorders*. Baltimore: Urban & Schwarzenberg, 1993:271–80.
9 **Putzke JD**, Richards JS, Hicken BL, *et al*. Interference due to pain following spinal cord injury: important predictors and impact on quality of life. *Pain* 2002;**100**:231–42.
10 **Uitti RJ**, Baba Y, Whaley NR, *et al*. Parkinson disease: handedness predicts asymmetry. *Neurology* 2005;**64**:1925–30.
11 **Louis ED**, Wendt KJ, Pullman SL. Is essential tremor symmetric? Observational data from a community-based study of essential tremor. *Arch Neurol* 1998;**55**:1553–9.
12 **Elbaz A**, Bower JH, Peterson BJ, *et al*. Survival study of Parkinson disease in Olmsted County, Minnesota. *Arch Neurol* 2003;**60**:91–6.
13 **Louis ED**, Barnes LF, Ford B, *et al*. Family history information on essential tremor: potential biases related to the source of the cases. *Mov Disord* 2001;**16**:320–4.