BMJ Open

Shaky drawing: what is the rate of decline during prospective follow-up of essential tremor?

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ABSTRACT

Objective: Few studies have attempted to estimate the rate of decline over time in essential tremor (ET). The study objectives were to: (1) measure change, deriving a single summary measure for the entire group, and relate it to a commonly used clinical rating scale (ie, yearly change in points on that scale); (2) to assess change as a function of baseline clinical characteristics and (3) to answer the basic clinical question—is change perceptible/obvious during the follow-up of ET cases?

Setting: Prospective collection of longitudinal data on ET cases enrolled in a study of the environmental epidemiology of ET at Columbia University Medical Center (2000–2008).

Participants: 116 unselected ET cases.

Interventions: Each case underwent the same evaluation at baseline and during one follow-up visit (mean follow-up interval (range)=5.8 (1.4–12.4) years).

Primary and secondary outcome measures: We assessed tremor during a commonly affected daily activity—drawing (ie, spirography), quantifying tremor using a simple, standardised 10-point rating scale developed by Bain and Findley.

Results: The Bain and Findley spiral score increased at an average rate of 0.12 ± 0.23 points per year (maximum=1 point/year). In cases who had been followed for ≥5 years, the change was obvious—a blinded neurologist was able to correctly order their spirals (baseline vs follow-up) in three-fourth of cases. The rate of change was higher in cases with versus without familial ET ($p=0.01$).

Conclusions: Tremor in ET is slowly progressive; yet in the majority of cases, a clear difference in handwritten spirals was visible with a follow-up interval of five or more years. There may be differences between familial and non-familial ET in the rate of progression. These clinical data are intended to aid in the prognostic discussions that treating physicians have with their patients with ET.

INTRODUCTION

By most accounts, essential tremor (ET) is a progressive neurological disease.[1] Nevertheless, only three papers have attempted to estimate the rate of decline over time.[2–4] Given the very

Strengths and limitations of the study

- Its prospective nature, the ability to assess cases with a broad range of follow-up intervals, the use of a reliable and validated 10-point rating scale and the use of an unbiased sample of essential tremor (ET) cases that were not self-selected.
- Cases were evaluated at two time points; additional time points would have added to the precision of our estimates.
- The study provides clinical data that are intended to aid in the prognostic discussions that treating physicians have with their patients with ET.

high prevalence of ET,[5] the relative dearth of longitudinal data is surprising. There is also the issue of selection bias. Patients who elect to return for follow-up clinical visits are a self-selected group who often have tremor that is progressively worsening; patients with stable tremor are less inclined to return.[4] Hence, studies that are clinic-based[2,3] are likely to overestimate the rate of decline in ET. One prior study used unselected cases.[4]

We prospectively collected longitudinal data on 116 ET cases who were not self-selected for follow-up based on a need for clinical care. They underwent the same evaluation at baseline and at one follow-up visit (mean follow-up interval (range)=5.8 (1.4–12.4) years). To maximise the clinical relevance of our results, we chose to assess tremor during a commonly performed, functionally relevant activity—drawing. Such tremor is plainly evident to clinicians, visible to patients and easily quantifiable using a simple, standardised, ordinal 10-point rating scale developed by Bain and Findley.[6]

The study addressed three a priori aims. First, to measure change, deriving a single summary measure for the entire group and relating it to a commonly used clinical rating scale (ie, yearly change in points on that scale).[6] Second, to assess change as a function of baseline clinical characteristics (age,

duration and tremor severity). Third, to answer the basic clinical question—is change perceptible/obvious during the follow-up of unselected ET cases?

METHODS
Participants and evaluation
Three hundred and seventy-six ET cases were enrolled in a research study of the environmental epidemiology of ET at Columbia University Medical Center (CUMC; 2000–2008).[7] [8] Cases had all received a diagnosis of ET from their treating neurologist and were confined to a geographical area that was within 2 h driving distance of CUMC.[4] Each case signed a written informed consent form approved by the CUMC Ethics Committee.

Cases completed clinical questionnaires and, as described,[9] 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 centred at right angles directly in front of them and held down by their other hand. Participants were instructed to hold the pen normally/comfortably, and not to anchor their writing hand/arm on the paper or table. This was repeated once, and then also performed twice with the non-dominant hand, yielding four spirals.

To confirm diagnoses and allow for a tremor rating, cases also underwent a standardised videotaped tremor examination, which included one test of postural tremor and five tests of kinetic tremor (eg, writing, pouring). Each test was performed with the dominant and non-dominant arms (12 tests in total).[4] The videotaped tremor examination also included assessments of rest tremor, voice tremor and head (neck) tremor. Each videotape was reviewed by a senior neurologist specialising in movement disorders (EDL), who rated the arm tremor during the 12 tests using a 0–3 scale with established intrarater and inter-rater reliability.[10] Based on the ratings, a total tremor score (0–36 (maximum)) was assigned. Using the clinical questionnaire and videotape data, the diagnosis of ET was reconfirmed in each case using published diagnostic criteria (moderate or greater amplitude kinetic tremor (tremor rating ≥2) during three or more activities or a head tremor in the absence of Parkinson's disease).[11]

In April 2009, we began conducting follow-up assessments with the goal of enrolling 120–130 cases.[4] A random selection scheme was used. We enrolled 116 cases. During the follow-up assessment, cases signed informed consent approved by the CUMC Ethics Committee and underwent the same assessment as at baseline, including the production of four spirals. Diagnoses were also reconfirmed using published diagnostic criteria.[11]

Spiral rating
In 2013, the tremor in each spiral was rated (EDL) blinded to all clinical data including assessment type (baseline vs follow-up). The spirals were not rated in pairs (ie, the rater only saw a single spiral at a time). The neurologist used a reliable and valid ordinal clinical rating scale (0–10 (most severe)), with accompanying visual examples of each rating, published by Bain and Findley.[6] The two right-hand spirals were averaged (right spiral score, range 0–10), as were the two left-hand spirals (left spiral score, range 0–10). These four were averaged as well (total spiral score, range 0–10).

Statistical analyses
Analyses were performed in SPSS (V.20). We calculated the change in spiral score in each case by subtracting the follow-up spiral score from the baseline spiral score. The average rate of change per year was calculated in each case as the change in spiral score divided by the number of years between the two assessments. Spiral scores as well as the change in these scores were normally distributed; hence, parametric tests were used. Spiral scores at baseline and follow-up were compared using paired t tests (table 1). We tested for trends using linear regression analysis (table 2).

RESULTS
There were 116 ET cases (table 1). The mean follow-up interval (time from baseline to follow-up assessment) was

Table 1 Demographic and clinical characteristics of 116 ET cases

Characteristics	Data
Age (years)*	71.5±12.5 (range 28–96)
Female gender	59 (50.9)
Right handed	100 (86.2)
Education (years)	16.0±2.5
White race	110 (94.8)
Total tremor score*	20.1±6.2 (range 8–34)
Head (neck) tremor in examination*	41 (35.3)
Voice tremor on examination*	28 (24.1)
Tremor duration (years)*	31.0±17.8 (range 3–76)
Age of tremor onset (years)*	40.7±18.8 (range 1–82)
Family history of ET*	31 (26.7)
Total spiral score†	
Baseline	3.41±1.70
Follow-up	4.05±1.78
Right spiral score†	
Baseline	3.22±1.86 (3.26±1.86 in 100 right-handed cases)
Follow-up	3.76±1.89 (3.82±1.91 in 100 right-handed cases)
Left spiral score†	
Baseline	3.59±1.79 (3.13±1.95 in 16 left-handed cases)
Follow-up	4.35±1.91 (4.31±2.11 in 16 left-handed cases)

Values represent mean±SD (range) or number (percentage).
*Baseline value.
†Baseline versus follow-up value differed in the full sample of 116 cases (paired t test, p<0.001).
ET, essential tremor.

Table 2 Total spiral score change by duration of follow-up category

Duration of follow-up category (years)	Mean duration of follow-up (years)	Number of cases	Change in total spiral score*	Neurologist was able to correctly establish the order
≤2.5	1.9	9	0.39±1.11	4 of 9 (44.4%)
>2.5–5	3.7	40	0.44±0.88	23 of 40 (57.5%)
>5–7.5	6.3	37	0.76±0.83	26 of 37 (70.3%)
>7.5–12.4	9.3	30	0.87±1.09	23 of 30 (76.7%)
			p=0.039 (test for trend)†	p=0.029 (test for trend)‡

*Values represent mean±SD.
†Linear regression analysis in which the dependent variable was the change in total spiral score and the independent variable was the duration of follow-up category.
‡Linear regression analysis in which proportion of correctly ordered cases was the dependent variable and duration of follow-up category was the independent variable.

5.8±2.6 years, median=5.7 years, range=1.4–12.4 years. Mean spiral scores were higher at follow-up than at baseline (p<0.001, table 1).

The total spiral score increased an average of 0.65±0.95 points (range=3.0 point increase to 1.75 point decrease). This score increased in 81 (69.8%) cases, decreased in 21 (18.1%) cases and stayed the same in 14 (12.1%) cases. The change in total spiral score was marginally correlated with the number of years that had elapsed between the two assessments (Spearman's r=0.18, p=0.055).

The total spiral score increased at an average *rate* of 0.12±0.23 points per year (maximum=1 point/year). In 10% of cases, it increased at a rate ≥0.4 points/year. Cases were stratified by duration of follow-up into four groups (table 2). A linear regression analysis (dependent variable=change in total spiral score, independent variable = duration of follow-up category) indicated that there was a trend—the higher the duration of follow-up category, the greater the change in average spiral score (β=0.196, p=0.039). Cases who were followed for an average of ~one decade experienced an approximately one-point increase in the average spiral score during that time interval (table 2).

It is important to consider the effect of medications. Therefore, in a sensitivity analysis, we considered these effects. Fifty ET cases were not on ET medications either at baseline or at follow-up. In these cases, the mean total spiral score increased by 0.53±0.84 points (range=2.25 point increase to 1.5 point decrease), and the total spiral score increased at an average rate of 0.10±0.20 points per year. These results were similar to those for the entire group of 116 cases presented above. We also considered the effects of caffeine. Fifty-three ET cases had not used caffeine (eg, tea, coffee) on the day of either assessment. In these, the mean total spiral score increased by 0.60±0.88 points (range=2.75 point increase to 1.25 point decrease), and the total spiral score increased at an average rate of 0.10±0.16 points per year. These results were similar to those for the entire group of 116 cases presented above.

We assessed the clinical factors that predicted the rate of change. A series of linear regression models was performed in which average change in total spiral score per year was the dependent variable, and independent variables in different models included baseline demographic and clinical characteristics. In these models, rate of change was not associated with baseline age (β=−0.001, p=0.53), gender (β=0.026, p=0.55), years of education (β=0.009, p=0.29), white race (β=−0.12, p=0.24), baseline tremor duration (β=0.00005, p=0.97), baseline total tremor score (β=0.006, p=0.12), baseline head tremor on examination (β=−0.07, p=0.15) or baseline voice tremor on examination (β=0.047, p=0.356). However, rate of change was higher in ET cases with a family history of ET (β=0.12, p=0.01): the average rate of change in the total spiral score was 0.21±0.25 points/year in the 31 ET cases with a family history of ET vs 0.09±0.22 points/year in the 85 ET cases without a family history of ET (Student's t test=2.58, p=0.01).

For each case, the neurologist attempted to order the four baseline versus four follow-up spirals. Despite the modest yearly change (far less than 1 point), the assigned order was correct in 76 (65.5%) cases and incorrect in 18 (15.5%) cases. The rater was not able to establish the order in 22 (19%) cases. Among those who were followed for more than 7.5 years, the neurologist was able to correctly establish the order in three-fourth of cases, whereas in those who were followed for 2.5 years or less, the neurologist performed as well as the toss of a coin (correctly guessing the order in approximately half of the cases; table 2).

DISCUSSION
Although a widely held view is that ET progresses slowly over time, this view is supported largely by anecdotal evidence rather than published data on rate of progression. The current analyses were designed to furnish quantitative data on rate of progression.

In this study of more than 100 unselected ET cases, the Bain and Findley[6] spiral score increased at an average yearly rate of 0.12±0.23 points; cumulatively, this would amount to a 1 point worsening over a decade. On the one hand, this seems like a small change over time. On the other hand, among ET cases who were followed

for five or more years, the magnitude of the decline was visible enough for a neurologist to correctly assign the order of the spirals (baseline vs follow-up) in approximately three-fourth of cases. That is, handwritten spirals had perceptibly worsened on visual inspection.

The rate of change was higher in ET cases with a family history of ET than in ET cases without a family history of ET. While age of onset is earlier in familial ET cases,[12] we are not aware of other data to suggest that rate of progression differs in these two forms of ET. These results should be confirmed.

In a prior study, we presented data on a small subsample (44 or 1/3) of these cases; data on all 116 cases were not available at that time.[4] In those analyses, we quantified the total tremor score, a broad measure of action tremor, but did not publish separate data on drawing samples. The current study was undertaken in order to maximise the clinical relevance of the derived data. With this in mind, we chose to evaluate a commonly performed, functionally relevant activity—drawing. This is one that is often assessed and followed in treatment settings. We also wanted to answer the additional clinical question, how perceptible is change during the follow-up? In other words, could a blinded neurologist distinguish baseline from follow-up spirals? This is a question that had not been assessed in our prior study.

The study had limitations. First, cases were evaluated at two time points; additional time points would have added to the precision of our estimates. Second, the time between evaluations was not rigidly fixed; however, rather than being a drawback, this allowed for a broad range of follow-up intervals and the ability to separately view data according to duration of follow-up category. Third, all cases came from a single study; additional studies should assess the degree to which these estimates can be generalised. Fourth, we assessed spiral drawing rather than sentence writing, as samples of the latter were not as routinely available; although the tasks are very similar, sentence writing is more clinically relevant than spiral drawing. Finally, we assessed tremor with a clinical rating scale rather than quantitative computerised tremor analysis; the latter would not have been practical within the framework of a clinical epidemiological study. Clinical rating scales lack some degree of precision, and ordinal clinical rating scales do not provide a continuous measure of tremor severity. The study also had a number of strengths. First, the follow-up interval was not standardised; hence, we were able to assess cases with a broad range of follow-up intervals, conducting analyses that took advantage of this fact. Second, the evaluation was identical at each time point. Third, the study was a prospective study. Fourth, the study used a reliable and validated 10-point rating scale. All ratings were conducted by a senior movement disorders neurologist who was blinded to clinical details. Most important is that the study used an unbiased sample of ET cases that were not self-selected, as noted above.

In summary, tremor while drawing in ET, assessed using the Bain and Findley[6] spiral score, worsened at an average rate of 0.12±0.23 points per year. While modest, the deterioration was visibly perceptible; indeed, a clinical neurologist was able to successfully order the spirals (baseline vs follow-up) in three-fourth of cases who were followed for five or more years. There may be differences between familial and non-familial ET in rate of progression. These clinical data are intended to aid in the prognostic discussions that treating physicians have with their patients with ET.

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