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ORIGINAL ARTICLE

Longitudinal study of clinical and neurophysiological features in essential tremor

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Abstract

Background and purpose: Essential tremor (ET) is a common and heterogeneous disorder characterized by postural/kinetic tremor of the upper limbs and other body segments and by non-motor symptoms, including cognitive and psychiatric abnormalities. Only a limited number of longitudinal studies have comprehensively and simultaneously investigated motor and non-motor symptom progression in ET. Possible soft signs that configure the ET-plus diagnosis are also under-investigated in follow-up studies. We aimed to longitudinally investigate the progression of ET manifestations by means of clinical and neurophysiological evaluation.

Methods: Thirty-seven ET patients underwent evaluation at baseline (T0) and at follow-up (T1; mean interval ± SD = 39.89 ± 9.83 months). The assessment included the clinical and kinematic evaluation of tremor and voluntary movement execution, as well as the investigation of cognitive and psychiatric disorders.

Results: A higher percentage of patients showed tremor in multiple body segments and rest tremor at T1 as compared to T0 (all p-values < 0.01). At T1, the kinematic analysis revealed reduced finger-tapping movement amplitude and velocity as compared to T0 (both p-values < 0.001). The prevalence of cognitive and psychiatric disorders did not change between T0 and T1. Female sex, absence of family history, and rest tremor at baseline were identified as predictive factors of worse disease progression.

Conclusions: ET progression is characterized by the spread of tremor in multiple body segments and by the emergence of soft signs. We also identified possible predictors of disease worsening. The results contribute to a better understanding of ET classification and pathophysiology.

KEYWORDS
essential tremor, kinematic, neurophysiology, tremor classification

INTRODUCTION

Essential tremor (ET) is a common movement disorder characterized by bilateral upper limb postural and/or kinetic tremor with at least 3-year duration, with or without tremor in other body segments [1]. In addition to action tremor, other motor features, non-motor manifestations including cognitive and psychiatric disorders, as well as the so-called soft signs (i.e., neurological signs of uncertain significance) are frequently observed in ET [2–5]. The relation between ET-plus and ET progression is an under-investigated issue. In the most recent consensus statement, the concept of ET-plus was introduced to classify ET cases that have additional neurological signs of uncertain significance and relation to tremor that are not sufficient to make alternative diagnoses [1]. However, the concept of ET-plus is controversial. According to some authors, ET-plus could merely be an advanced stage of ET rather than a distinct condition with distinct pathophysiological mechanisms [6, 7], and the relation between soft signs and ET progression is unclear. To date, only one longitudinal study has specifically investigated ET-plus progression [7]. Further clarifying the occurrence of soft signs in ET progression may provide a better understanding of the ET-plus concept.

The progression of ET manifestations is still a critical and under-investigated issue. To date, only a few clinical longitudinal studies have characterized the progression of motor features in ET. Some studies estimated an annual tremor severity worsening of between 3.1% and 12% [8, 9], with tremor spread to cranial structures [10, 11]. Increased tremor severity over time may also depend on the higher prevalence of rest tremor observed in advanced disease stages [12]. The progression of non-motor symptoms in ET is even less understood [7, 13–16]. Regarding demographic and clinical factors possibly influencing ET progression, it has been shown that female patients have a higher risk of manifesting or developing head and voice tremor over time [17–19]. The contribution of other factors, including age at tremor onset, family history, or specific tremor characteristics at baseline, to disease progression has been poorly addressed [5, 20, 21]. Moreover, although some evidence showed a reduction in postural tremor frequency over time [22], no previous neurophysiological study has comprehensively assessed whether tremor features in ET, including tremor distribution and activation conditions, change during the disease course.

Here, we aimed to longitudinally investigate ET manifestations, with a focus on tremor features and body distribution over a 3-year period. In the same follow-up period, we also investigated the evolution of soft signs, including rest tremor, bradykinesia, questionable dystonia, impaired tandem gait, and mild cognitive impairment (MCI). Tremor and repetitive finger movement execution were evaluated by standardized clinical scales and a kinematic system for movement analysis. Non-motor manifestations (i.e., cognitive and psychiatric disorders) were also assessed to exclude possible influences on changes in motor symptoms. To identify possible predictive factors for ET progression, we considered patients' main clinical and demographic data and employed subgroup analyses and regression techniques.

MATERIALS AND METHODS

Participants

We recruited 37 ET patients from the outpatient clinic of the Department of Human Neurosciences, Sapienza University of Rome, diagnosed according to clinical criteria [1]. Patients under treatment for tremor were evaluated after drug withdrawal. In detail, therapy discontinuation was obtained by dose reduction in the week prior to evaluation, with drug withdrawal 24 h earlier for propranolol and benzodiazepines and 48 h earlier for primidone and topiramate. No patient underwent deep brain stimulation. All patients underwent magnetic resonance imaging during at least one evaluation, which showed no lesions indicative of alternative diagnoses. Patients underwent two sessions, one baseline (T0) and one follow-up session (T1), with an interval from T0 of 39.89 ± 9.83 months (mean $\pm$ 1 SD). Each session included clinical and kinematic assessment of tremor and repetitive finger movements, and the assessment of non-motor symptoms through cognitive and psychiatric evaluations. Experimental procedures were carried out in accordance with the Declaration of Helsinki and approved by the local ethics committee. Written informed consent to participate in the study was provided by all participants.

Clinical evaluation

Clinical and demographic data were collected. A neurological examination of tremor and soft signs in patients was conducted by a neurologist experienced in movement disorders (G.P.). Tremor was assessed using the Fahn–Tolosa–Marin Tremor Rating Scale (FTM-TRS) and the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III. Cognitive and psychiatric evaluations by clinical scales and interviews were also performed (Appendix S1). In accordance with the latest consensus statement [1], we considered soft signs to include rest tremor, slight bradykinesia, questionable dystonia, impaired tandem gait, and MCI. Patients who scored at least 1 on MDS-UPDRS scores 3.4–3.8, considering movement rhythm, slowness, and amplitude decrement, were considered to have bradykinesia. Questionable dystonia was defined by the presence of subtle sustained or intermittent muscle contractions causing abnormal movements, postures, or both [23]. Patients were considered to have impaired tandem gait if they made more than one misstep during the tandem gait task but managed to complete the task without a clearly pathological gait. Patients with an impairment in at least 50% of the neuropsychological tests in one or more domains were considered to have MCI.

Kinematic recordings and analysis of tremor and finger movements

We used an optoelectronic system (SMART motion system, BTS Engineering) with three infrared cameras with a sampling rate

TABLE 1 Demographic data of essential tremor patients at baseline (T0) and follow-up (T1) evaluations

Characteristic	T0	T1	*p*
Sex	17 Female/20 Male (45.95%/54.05%)	-	-
Age, years	66.27 ± 11.14	69.59 ± 10.93	**<0.01**
Age at onset, years	50.64 ± 18.51 (median = 56)	-	-
Tremor duration, years	15.64 ± 15.24	18.96 ± 15.31	**<0.01**
Family history	23 Y/14 N (62.16%)	-	-

Abbreviations: Y: yes; N: No.

Note: Data are given as mean ± SD of the mean. Significant *p*-values are shown in bold.

of 120 Hz that followed the three-dimensional displacement of reflective markers taped to the patients' head, trunk, and arms [5, 24, 25].

Upper limb postural, rest, and kinetic tremor, and head tremor were recorded as detailed in previous studies (see also Appendix S1) [5, 24, 25]. Upper limb postural tremor was recorded during two postures, with the arms outstretched in front of the chest (Posture 1 [P1]) and with the arms flexed at the elbows (i.e., lateral "wing-beating" posture; Posture 2 [P2]). Tremor analysis was performed using dedicated software (SMART Analyzer, BTS Engineering; Appendix S1) [24, 26].

For finger-tapping recordings, participants performed three 15-s trials of repetitive finger movements with both hands [25, 27]. Movement analysis was performed to determine a number of kinematic parameters (Appendix S1) [25].

Statistical analysis

Categorical variables were expressed as frequencies and compared using McNemar test. Numerical variables recorded at T0 and T1 were compared using Wilcoxon signed-rank test. The kinematic values of upper limb postural tremor amplitude and frequency were analysed in two separate repeated-measures analyses of variance (rmANOVAs), using the factors TIME (two levels: T0 and T1) and POSTURE (two levels: P1 and P2). Fisher least significant difference test was used for post hoc analyses. Paired *t*-tests were used to compare kinematic parameters of upper limb rest and kinetic tremor and head tremor recorded at T0 and T1. Finger-tapping kinematics were also compared by paired *t*-tests. The average of the values from the two body sides was used.

A subgroup analysis was performed by dividing patients according to sex, family history of tremor, age at onset > 60 years (late adulthood, according to the latest consensus statement on the classification of tremors [1]), baseline presence of head or rest tremor, single or multiple body segment involvement, and asymmetric tremor. For quantitative clinical data, we calculated the *longitudinal variation* by dividing the percentage variation of different scores by years of follow-up for each patient [9]. We then compared quantitative data in the subgroups with Mann–Whitney *U*-test. These subgroups were also used as between-subject factors in different rmANOVAs to analyse differences in kinematic values of upper limbs and head tremor, and finger-tapping.

TABLE 2 Tremor clinical data of essential tremor patients at baseline (T0) and follow-up (T1) evaluations

Scale	T0	T1	*p*
FTM-TRS total	19.9 ± 10.58	29.19 ± 13.07	**<0.01**
FTM-TRS Section A	6.95 ± 3.41	10.05 ± 5.05	**<0.01**
FTM-TRS Section B	8.40 ± 5.29	12.48 ± 6.04	**<0.01**
FTM-TRS Section C	4.56 ± 3.37	6.60 ± 4.54	**<0.01**
MDS-UPDRS III total	6.41 ± 3.66	11.79 ± 8.27	**<0.01**

Abbreviations: FTM-TRS, Fahn–Tolosa–Marin Tremor Rating Scale; MDS-UPDRS III, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale Part III.

Note: Data are given as mean ± SD of the mean. Significant *p*-values are shown in bold.

Different multivariate linear regression analyses were performed to determine whether clinical and kinematic variation parameters of tremor severity and finger-tapping execution (dependent variables) depended on demographic and clinical data (sex, family history of tremor, age at T0, age at onset > 60 years, tremor duration, FTM-TRS score at T0, baseline presence of head tremor, rest tremor, or asymmetric tremor of the upper limbs, or number of body parts involved at T0—independent variables). Predictive variables were selected through a stepwise method.

All results are presented as mean value ± 1 SD unless otherwise specified. The level of significance was set at $p < 0.05$. Data were analysed using Statistica (TIBCO Software) and SPSS Statistics for Windows v26.0 (IBM, released 2019).

RESULTS

Baseline data

Main demographic data are shown in Table 1. All patients with positive family history for tremor had an affected first-degree family member, and no difference in age at tremor onset was observed between patients with and without a family history for tremor (47.5 vs. 55.79 years, respectively; $p = 0.18$). Drug therapy data are shown in Table S1. Table 2 depicts FTM-TRS and MDS-UPDRS Part III scores (detailed scores are shown in Tables S2 and S3).

At T0, all patients had postural and/or kinetic tremor in the upper limbs. Twenty-one of 37 patients (56.76%) had upper limb tremor

only, whereas 16 of 37 patients (43.24%) had upper limb tremor in combination with tremor in other body segments (Figure 1).

Cognitive and psychiatric disorders were present in the same percentage of patients (20/37, 54.05%) at T0 (Table 3). The most represented MCI subtypes were non-amnestic single-domain MCI and amnestic multidomain MCI. The most involved cognitive domains were executive function and memory. Anxiety and depression were the most frequent psychiatric disorders observed.

At T0, 30 of 37 patients (81.08%) had one or more soft signs (Figure 2).

Symptom progression

Clinical data

FTM-TRS total scores significantly increased from T0 to T1 ($p < 0.01$; Table 2), with a 71% ±91.43% increase (median value = 52%). All FTM-TRS subscores increased over time (all p-values <0.01). Comparing T0 and T1, the presence of tremor in body segments other than the upper limbs increased ($p < 0.01$; Figure 1). Tremor severity during different complex tasks (drawing spirals and several activities of daily living) increased at T1, whereas clinical scores of postural tremor of the upper limbs showed no change at T1 (Table S2). Notably, the number of ET patients with rest upper limb tremor also increased at T1 ($p < 0.01$; Figure 2).

The MDS-UPDRS Part III score increased between the two evaluations ($p < 0.01$; Table 2), with differences in bradykinesia, posture, and rest tremor subscores (Table S3).

Mini-Mental State Examination scores did not change between T0 and T1 ($p = 0.64$). MCI, being present in 20 of 37 patients (54.05%) at T0, was detected in 21 of 35 patients (56.76%) at T1 ($p = 1$; Table 3). No patients developed dementia at T1. Psychiatric disorders did not change over time (Table 3). The Hamilton Depression Rating Scale showed a trend toward reduction between the two evaluations ($p = 0.06$; Table 3).

The number of ET-plus patients increased from 30 of 37 (81.08%) at T0 to 36 of 37 (97.3%) at T1 ($p < 0.01$), with an increase in the prevalence of rest tremor, bradykinesia, and impaired tandem gait (Figure 2). Most of the soft signs were in combination with each other.

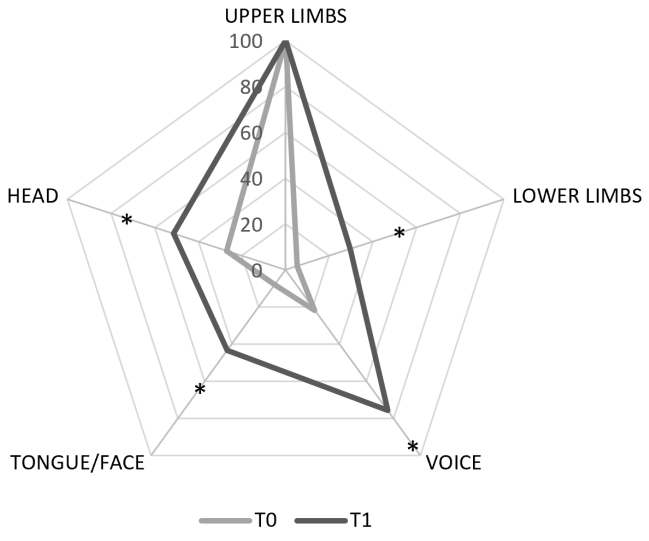

FIGURE 1 Topographic tremor distribution in patients with essential tremor (ET). Percentage of ET patients with tremor in different body segments at baseline (T0) and follow-up (T1) evaluations are shown according to the clinical assessment. Asterisks indicate significant p-values

Kinematic data

Data are shown in Table 4. Analysis of postural tremor amplitude showed a significant effect of POSTURE ($F_{1, 72} = 9.59$, $p < 0.01$), with higher tremor amplitude in P2 compared to P1 at both T0 and T1. No significant interaction TIME*POSTURE was found ($p > 0.05$). Analysis of postural tremor frequency also showed a significant effect of POSTURE ($F_{1, 72} = 5.33$, $p = 0.02$), and there was no significant TIME*POSTURE interaction ($p > 0.05$). Post hoc comparison only showed higher tremor frequency for P2 at T0 than for P1 at T1.

The analysis of rest tremor showed an increase in tremor frequency ($p = 0.02$) at T1 without amplitude variations, probably due to the low constancy of rest tremor during the evaluation. No difference emerged in the comparison of upper limb kinetic tremor and head tremor (all p-values >0.05).

Finger-tapping kinematic analysis revealed a reduction in movement amplitude and velocity (both p-values <0.01) at T1 as compared to T0, with a reduction in velocity slope. No difference in other kinematic parameters was found (all p-values >0.05).

Predictive factors of disease progression

Subgroup analysis

In analysis by sex (17 females vs. 20 males), females showed a higher number of body segments involved at T1 (3.88±1.5, median = 4, interquartile range [IQR] =2) than males (2.65±1.39, median = 2.5, IQR= 2.5; $p = 0.02$).

In analysis by family history of tremor (14 patients with no family history vs. 23 patients with a positive family history), patients with no family history, when compared with those with positive family history, showed a greater longitudinal variation in the total FTM-TRS score (39.16%±48.34%, median = 20.07%, IQR = 42.72% vs. 14.05%±16.47%, median = 10.1%, IQR = 18.31%; $p = 0.04$) and in the tremor amplitude in P2 at kinematic analysis (15.97%±46.95%, median = -2.29%, IQR = 49.26% vs. −6.57%±18.22%, median = −9.7%, IQR = 12.49%; $p = 0.04$). Comparison of FTM-TRS scores at T0 revealed no differences in these subgroups (all p–values >0.05).

In analysis by rest tremor at T0 (27 patients with rest tremor vs. 10 patients without rest tremor), patients with baseline rest tremor, when compared with those without rest tremor, showed a

TABLE 3 Cognitive and psychiatric data of ET patients at baseline (T0) and follow-up (T1) evaluations

Data	T0	T1	*p*
Cognitive data			
MMSE	27.65 ± 0.95	27.33 ± 2.62	0.646
ET-MCI, *n* of patients	20 Y/17 N (54.05%)	21 Y/16 N (56.76%)	0.62
a-MCI	3 Y/34 N (8.11%)	3 Y/34 N (8.11%)	1
a-MCI+	10 Y/27 N (27.03%)	5 Y/32 N (13.51%)	**<0.01**
na-MCI	7 Y/30 N (18.92%)	10 Y/27 N (27.03%)	**<0.01**
na-MCI+	0 Y/37 N (0%)	3 Y/34 N (8.11%)	**<0.01**
Cognitive domains altered, *n*	0.81 ± 0.84	0.84 ± 0.96	0.14
Executive function	13 Y/24 N (35.14%)	18 Y/19 N (48.65%)	0.38
Attention	6 Y/31 N (16.22%)	3 Y/34 N (8.11%)	**<0.01**
Memory	11 Y/26 N (29.73%)	8 Y/29 N (21.62%)	**0.01**
Visuoconstructional	2 Y/35 N (5.41%)	2 Y/35 N (5.41%)	1
Psychiatric data			
Psychiatric disorders, *n* of patients	20 Y/17 N (54.05%)	14 Y/23 N (37.84%)	0.24
Anxiety	13 Y/24 N (35.14%)	11 Y/26 N (29.73%)	0.8
Depression	7 Y/30 N (18.92%)	2 Y/35 N (54.05%)	0.15
Bipolar disorder	0 Y/37 N (0%)	1 Y/36 N (2.7%)	1
HAM-A	8.41 ± 7.08	5.97 ± 5.06	0.64
HAM-D	7.59 ± 6.52	4.81 ± 4.14	0.060
BPRS	29.16 ± 4.69	28.81 ± 3.96	0.81
CGI-S	1.84 ± 0.87	1.57 ± 0.83	0.15

Abbreviations: a-MCI, amnestic single domain MCI; a-MCI+, amnestic multidomain MCI; BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression–Severity Scale; ET, essential tremor; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; N, no; na-MCI, non-amnestic single-domain MCI; na-MCI+, non-amnestic multidomain MCI; Y, yes.

Note: Data are given as the number of patients having cognitive and psychiatric disorders, or alternatively, as mean ± SD of the mean. Percentages are indicated in parentheses. Significant *p*-values are shown in bold.

greater longitudinal variation in the number of body segments involved (75.61% ± 69.98%, median = 53.96%, IQR = 126.07% vs. 28.88% ± 32.49%, median = 17.39%, IQR = 58.65%; $p = 0.04$) and a worsening of tremor amplitude in P1 (longitudinal variation: 8.76% ± 35.27%, median = −1.95%, IQR = 21.09% vs. −11.08% ± 8.87%, median = −11.74%, IQR = 12.42%; $p < 0.01$) and P2 (longitudinal variation: 21.1% ± 45.91%, median = −1.65%, IQR = 75.15% vs. −5.13% ± 25.11%, median = −11.91%, IQR = 15.12%; $p = 0.03$) on kinematic analysis. In patients with baseline rest tremor, ANOVA confirmed higher postural tremor amplitude in P1 and P2 ($p = 0.01$ and $p = 0.03$, respectively) and showed a reduction in finger-tapping number of movements (TIME*PRESENCE OF REST TREMOR: $F_{1, 35} = 5.18$, $p = 0.03$).

Multivariate regression analysis

Multivariate linear regression analysis data are shown in Table 5. Longitudinal variation in FTM-TRS total score showed a negative association with T0 FTM-TRS total score. The longitudinal variation in the number of body segments involved showed a positive association with the presence of rest tremor at T0 and a negative association with the number of body segments involved at T0. The longitudinal variation of tremor amplitude in P1 and P2 at kinematic analysis showed a positive association with the presence of rest tremor at T0, and only for P2 also with absence of family history. The longitudinal variation in finger-tapping amplitude showed a positive association with age at T0.

DISCUSSION

In the present paper, we found that demographic and clinical data collected at baseline in our sample were consistent with those previously described [28]. By definition, all patients presented upper limb postural and/or kinetic tremor, but a considerable proportion also had tremor in other body segments, with the head being the most involved segment [5, 18]. More than half of patients had a family history of tremor [29]. Cognitive and psychiatric disorders were also observed, confirming a higher prevalence of MCI in ET

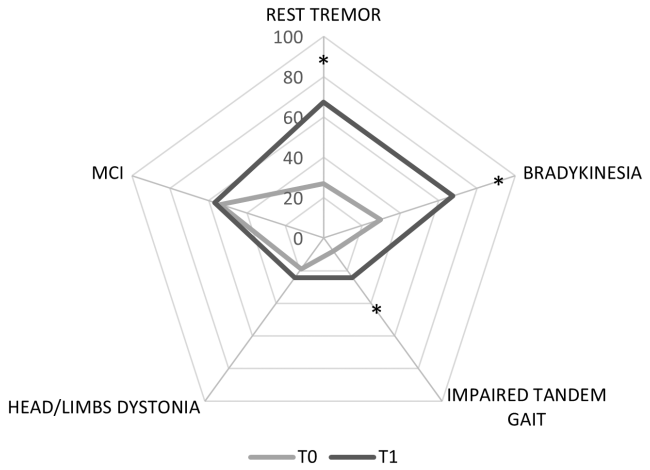

FIGURE 2 Soft signs in patients with essential tremor (ET). Percentage of ET patients with different soft signs at baseline (T0) and follow-up (T1) evaluations are shown according to the clinical assessment. Asterisks indicate significant *p*-values. MCI, mild cognitive impairment

than in the general population [30], with executive function and memory being the most involved domains [31, 32]. We also found that anxiety and depression were more common in ET than in normal subjects, in line with previous evidence [3]. Finally, consistent with previous data, 80% of patients presented soft signs [1], including rest tremor, subtle bradykinesia and dystonia [33], impaired tandem gait, and MCI, and thus could be categorized as ET-plus [29, 34–36]. At follow-up evaluation, we found that tremor severity in ET increased, with tremor spread in different body segments and a worsening of tremor during specific complex tasks (i.e., drawing spirals and several activities of daily living). Conversely, non-motor manifestation prevalence and severity did not change. Various clinical and demographic features (e.g., female sex, absence of family history, and baseline rest tremor) were identified as possible predictive factors of disease worsening. Finally, we also found a higher prevalence of soft signs (i.e., rest tremor, bradykinesia, and impaired tandem gait) over time.

Given the appropriate discontinuation of drug therapy and the lack of evidence of disease-modifying effects of the main drugs used in ET, any influence of therapeutic changes on our results can be ruled out. ET diagnosis was based on clinical criteria [1], and patients did not undergo DaTscan. However, disease duration was at least 3 years, and no patients showed signs suggestive of other possible diagnoses, including parkinsonism. Finally, the lack of cognitive and psychiatric changes allowed us to exclude that the worsening of motor manifestations was due to the influence of non-motor disorders.

We found that ET worsened over time mainly due to a progressive topographical spread of tremor, with the involvement of other segments besides upper limbs. Conversely, tremor amplitude and frequency in the body segment originally involved did not change over time, as demonstrated by kinematic analysis. We also demonstrated clinical evidence of tremor worsening in complex motor tasks not recorded by kinematics, including drawing spirals and different activities of daily living. Notably, we found an inverse relationship between baseline tremor severity, in terms of FTM-TRS score and the number of body segments involved, and the longitudinal changes of these two parameters. The more severe and widespread the tremor at baseline, the less tremor worsening observed over time. Concerning non-motor symptoms, we did not find clear changes in cognitive or psychiatric features over time. To date, only a few longitudinal studies have assessed whether non-motor symptoms progressed in ET, showing a worsening of cognitive performance and a high conversion rate to dementia in ET patients with MCI [13–15]. Differences in sample size and follow-up duration may explain the discrepancies in cognitive worsening over time between studies. Conversely, our observation of substantial psychiatric profile stability in ET over time is in line with the only study on the subject [13].

When investigating predictive factors of ET worsening, we found that females showed a spread of tremor over time. These results are consistent with previous data showing higher involvement of cranial district in female patients [17–19, 37]. Again, patients without a family history of ET showed a higher increase in tremor severity over time, despite similar baseline tremor severity when compared with patients with a family history. Finally, baseline rest tremor also negatively influenced disease progression. Our data are relevant because they derive from a longitudinal evaluation rather than a cross-sectional or retrospective study, and overall support the hypothesis that female patients without a family history for tremor and with rest tremor may represent a peculiar phenotype of ET, with a higher risk of disease progression over time.

Regarding the ET-plus concept, the number of patients with rest tremor, bradykinesia, and impaired tandem gait increased at the follow-up evaluation, thus the overall percentage of ET-plus was higher at follow-up as compared to baseline. To date, only one longitudinal study has specifically investigated ET-plus progression [7]. It showed that the prevalence of ET-plus progressively increased from 58.7% to 72.1% in a 54-month follow-up [7], with impaired tandem gait, memory impairment, and rest tremor being the most frequent soft signs. Although the percentage of ET-plus at baseline differed between our study and that by Iglesias-Hernandez, possibly due to the variable and questionable nature of soft signs, the rate of conversion from ET to ET-plus was similar in the two studies.

Our results have pathophysiological implications. It is well established that the cerebellum plays a major pathophysiological role in ET [38–42]. The observation that ET progressed over time because it spread in multiple body segments and worsened during the execution of complex tasks, as well as the evidence of an increase in tandem gait impairment, may indicate more extensive cerebellar involvement in the disease course [38, 42, 43]. From this perspective, tremor progression may be interpreted as being related to progressive cerebellar neurodegeneration [38, 42], although some results are controversial, such as the absence of intentional tremor worsening. Moreover, the presence of rest tremor and bradykinesia configuring the diagnosis of ET-plus, and the progression of these manifestations over time, may reflect a progressive involvement of the basal ganglia and

TABLE 4 Kinematic data of tremor and repetitive finger-tapping in essential tremor patients at baseline (T0) and follow-up (T1) evaluations

	T0	T1	*p*
Postural tremor			
P1			
GRMS^2	0.33 ± 0.21	0.28 ± 0.43	0.43
Hz	4.67 ± 1.57	4.08 ± 1.99	0.06
P2			
GRMS^2	0.71 ± 1.2	0.61 ± 1.12	0.38
Hz	6.41 ± 7.53	5.27 ± 1.14	0.38
Rest tremor			
GRMS^2	0.12 ± 0.07	0.11 ± 0.13	0.68
Hz	7.72 ± 2	10.05 ± 5.97	**0.02**
Head tremor			
GRMS^2	0.14 ± 0.13	0.12 ± 0.11	0.27
Hz	4.8 ± 1.08	5.16 ± 2.02	0.33
Pointing task			
Movements, *n*	9.49 ± 2.9	10.48 ± 2.52	0.09
Distance, m	0.46 ± 0.1	0.42 ± 0.07	0.11
Velocity peak, m/s	1.49 ± 0.9	1.4 ± 0.31	0.51
Acceleration peak, m/s^2	14.23 ± 8.4	15.69 ± 7.28	0.29
D/A	0.64 ± 0.33	0.52 ± 0.13	0.06
CI	1.06 ± 0.04	1.07 ± 0.04	0.38
Finger-tapping			
Movements, *n*	40.7 ± 11.62	38.62 ± 9.55	0.28
CV	0.1 ± 0.04	0.1 ± 0.03	0.21
Amplitude, °	47.56 ± 8.92	36.97 ± 12.24	**<0.01**
Velocity, °/s	990.92 ± 232.68	857.67 ± 279.99	**<0.01**
Amplitude slope, °/movements, *n*	0.11 ± 0.16	0.08 ± 0.2	0.35
Velocity slope (°/s)/movements, *n*	6.15 ± 3.766	4.03 ± 4.47	**0.01**

Abbreviations: CI, curvature index; CV, coefficient of variation; D/A, deceleration/acceleration ratio; P1, Posture 1 (arms outstretched in front of the chest); P2, Posture 2 (arms flexed at the elbows, i.e., lateral "wing-beating" posture).

Note: Tremor amplitude is expressed by the root mean square of the acceleration traces of the reference marker in three-dimensional space (GRMS^2). Tremor frequency is expressed in Hz. Kinetic tremor was evaluated during the pointing task. Data are expressed as mean ± SD of the mean. Significant *p*-values are shown in bold.

connections between the basal ganglia and cerebellum [44]. In this regard, it should be noted that our patients did not undergo DaTscan, which would have helped clarify the possible presence of dopaminergic alterations. Some evidence suggests a possible overlap between ET and Parkinson disease [45], but previous studies demonstrated that the conversion from ET to Parkinson disease is relatively limited [45, 46]. Furthermore, cerebellar dysfunction itself could explain the presence of bradykinesia in ET, as demonstrated by previous studies [47]. Regardless of the pathophysiological background, whether ET-plus represents a specific subtype of ET or a stage of the disease remains an open question. We here found that the percentage of ET-plus patients increased over time. Together with previous, but not all [29] observations coming from cross-sectional and retrospective studies [6, 7, 48, 49], our findings may overall support the hypothesis that ET-plus can be considered an advanced stage of the disease rather than a distinct entity. Accordingly, a recent study found no differences in pathological cerebellar findings between ET-plus and ET patients [48]. However, ET-plus remains a controversial entity [50]. Thus, further evidence is needed to clarify the present issues.

The present study has some limitations. The relatively limited sample size could have influenced the results, particularly the clinical results concerning cognitive and psychiatric disturbances and gait disorders, and the subgroup analysis, that should be considered as descriptive. Although the presence of only one examiner may be a limitation, using the same investigator for both evaluations limited interrater variability.

TABLE 5 Multivariate linear regression analysis data

	R^2	Standard error	Overall *F*-test *p*	Beta-coefficient	*p*
Longitudinal variation of FTM-TRS total score	0.262	0.797	**<0.01**		
FTM-TRS score at T0				−0.512	**<0.01**
Longitudinal variation of number of body segments involved	0.278	1.218	**<0.01**		
Presence of rest tremor at T0				0.33	**0.03**
Number of body segments involved at T0				−0.381	**0.01**
Longitudinal variation of P1 GRMS^2	0.15	0.718	**0.02**		
Presence of rest tremor at T0				0.387	**0.02**
Longitudinal variation of P2 GRMS^2	0.254	0.783	**0.01**		
Absence of family history				0.324	**0.04**
Presence of rest tremor at T0				0.378	**0.02**
Longitudinal variation of finger-tapping amplitude	0.159	0.349	**0.02**		
Age at T0				0.398	**0.02**

Abbreviations: FTM-TRS, Fahn–Tolosa–Marin Tremor Rating Scale; GRMS^2, tremor amplitude expressed by the root mean square of the acceleration traces of the reference marker in three-dimensional space; P1, Posture 1 (arms outstretched in front of the chest); P2, Posture 2 (arms flexed at the elbows, i.e., lateral "wing-beating" posture).

Note: Annual variations of different clinical and kinematic parameters represent the dependent variables. Several demographic and clinical parameters at baseline (T0) evaluation represent the independent variables. All predictors included as independent variables in different models have been included in the table. Significant *p*-values are shown in bold.

In conclusion, this longitudinal clinical and neurophysiological evaluation of ET manifestations provided novel information on ET progression, predictors of disease worsening, and the significance of soft signs. The results are relevant in the debate on ET classification and pathophysiology.

AUTHOR CONTRIBUTIONS

Luca Angelini: Conceptualization, investigation, data curation, formal analysis, writing—original draft preparation. **Giulia Paparella:** Conceptualization, investigation, data curation, writing—original draft preparation, writing—review & editing. **Alessandro De Biase:** Investigation, data curation. **Annalisa Maraone:** Investigation, data curation. **Matteo Panfili:** Investigation, data curation. **Isabella Berardelli:** Investigation, data curation. **Antonio Cannavacciuolo:** Investigation, data curation. **Antonella Di Vita:** Investigation, data curation. **Roberta Margiotta:** Investigation, data curation. **Giovanni Fabbrini:** Supervision. **Alfredo Berardelli:** Writing—review & editing, supervision. **Matteo Bologna:** Conceptualization, formal analysis, writing—review & editing, supervision.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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