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ORIGINAL PAPER

Tremor Distribution and the Variable Clinical Presentation of Essential Tremor

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Abstract

In addition to having postural and kinetic tremor of the upper limbs, some patients with essential tremor (ET) may have head tremor as well as cognitive and psychiatric disorders. We aimed to investigate whether the variable clinical presentation in ET patients, including motor and non-motor symptoms, differs in patients with and without head tremor. We consecutively enrolled 70 patients with a diagnosis of ET. Tremor severity was assessed by means of clinical rating scales. Patients also underwent kinematic recordings of postural and kinetic tremor of the upper limbs based on an optoelectronic system. Several neuropsychological tests were also administered. Finally, we adopted the structured interviews for DSM-IV, SCID-I, and SCID-II to investigate psychiatric and personality disorders. ET patients with upper limb tremor plus head tremor exhibited more severe kinetic tremor of the upper limbs and a higher occurrence of axis I psychiatric disorders than ET patients with upper limb tremor only. Cognitive and other motor and psychiatric features did not differ significantly with respect to tremor distribution. The study findings support the hypothesis that body tremor distribution, i.e., the presence of head tremor, influences the variable clinical presentation of ET. The study results support the notion that cases with head tremor may represent a distinct ET subtype, characterized by a prominent cerebellar involvement, and that psychiatric disorders should be considered as a specific manifestation of ET.

Keywords Essential tremor · Head tremor · Cognitive disorders · Psychiatric symptoms · Neurophysiology

Introduction

Essential tremor (ET) is a common movement disorders characterized by postural and kinetic tremor of the upper limbs and of other body segments [1–4]. When additional neurological signs of uncertain relationship to tremor (i.e., "soft neurological signs") are present, including cognitive or psychiatric abnormalities [5, 6], the recent classification of tremor suggest using the term ET-plus [3].

As recently pointed out, the clinical phenomenology of ET may considerably vary in terms of body tremor distribution and head tremor can be present in up to 1/3 of ET cases [2, 3, 7]. The presence of head tremor in ET is relevant because this feature is thought to be a manifestation of more severe cerebellar dysfunction. For example, neuroimaging studies in human patients with ET indicate that the cerebellum is involved in ET cases with head tremor to a greater extent than in cases without head tremor [8, 9]. Again, post-mortem studies indicate that ET patients with head tremor had more severe pathological changes in the cerebellar vermis [10, 11]. Because the cerebellum is a critical pathophysiologic node in the generation and expression of tremor as well as cognitive or psychiatric abnormalities [12], it is conceivable that ET patients with head tremor exhibit more severe clinical features than those without head tremor. Accordingly, it has been demonstrated that head tremor in ET may be associated with longer duration and higher severity of upper limb tremor, as assessed by

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clinical examination [7, 13]; however, there is still no neurophysiological study confirming these clinical observations. Moreover, the extent to which the presence of head tremor in ET is associated with cognitive or psychiatric abnormalities in ET is largely unexplored.

To further investigate the variable clinical presentation of symptoms in ET with and without head tremor, we here collected demographic, clinical, and kinematic data from a relatively large sample of ET patients. We then investigated whether tremor features as well as cognitive or psychiatric abnormalities differ in ET patients with and without head tremor. A better understanding of this issue may provide further insight into the variable clinical presentation of ET and allow specific disease-related features to be distinguished from coincidental findings or age-related epiphenomena [11].

Patients and Methods

Patients

Patients were recruited prospectively from the movement disorders outpatient clinic of the Department of Human Neurosciences, Sapienza University of Rome, from February 2017 till December 2018. We enrolled 70 patients (29 females) with a clinical diagnosis of ET made according to established clinical criteria [3]. None of the ET cases had a history of traumatic brain injury, current or previous exposure to medications, heavy ethanol uses, or clinically detectable associated signs of systemic or neurologic illness, including movement slowness (bradykinesia), dystonia, and ataxia. Patients being treated were tested at least 48 h after medication withdrawal. The local institutional review board approved the experimental procedures and all the participants gave their written informed consent to the study. Authorization has been obtained for disclosure of any recognizable persons in videos. The experiments adhered to the regulations laid down in the Declaration of Helsinki.

Tremor Assessment

Clinical Evaluation

Each patient underwent a neurological examination, which included a detailed assessment of tremor by means of the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS) [14–16], sections A–C. We then calculated the global score (FTMTRS total score) and three subscores for each part of the scale.

Kinematic Recordings and Analysis

Kinematic recordings were performed using an optoelectronic system (SMART motion system, BTS Engineering, Italy). Subjects were seated on a chair facing three infrared cameras (sampling rate of 120 Hz) that followed the 3D displacement of reflective markers of negligible weight taped to the subject's head, trunk, and arms [17, 18]. Postural limb tremor was recorded during the forward "horizontal" reach posture. Three 45-s recordings were obtained per patient. Kinetic tremor was recorded during three 15-s recordings while subjects were asked to repetitively move their index finger from their nose to a reflective target fixed on a heavy support approximately 15 cm above the table at sternal height and 2/3 arm distance ("pointing task").

Tremor analysis was performed using dedicated software (SMART Analyzer, BTS Engineering, Italy). We determined the magnitude of tremor by measuring the root-mean-square (RMS) of the acceleration traces of the reference markers in 3D space. The postural tremor magnitude was then expressed in GRMS^2 [17–21]. Power spectra were calculated by means of fast Fourier transformation. We then measured the dominant frequency peak (Hz) of postural tremor [17–21]. Another algorithm was used to measure kinetic tremor of the upper limb. We determined number of movements, distance (m), velocity peak (m/s), and acceleration peak (m/s^2), deceleration/acceleration ratio—D/A (i.e., duration of the deceleration phase/duration of the acceleration phase) and the curvature index—CI (i.e., arm endpoint average path length/length of a straight line joining the initial and final positions). The last two parameters served as indexes of movement homogeneity [18, 20, 22].

Cognitive Assessment

The neuropsychological test battery was designed specifically for the study by a neuropsychologist. The battery included measures of global cognition (Mini-Mental State Examination) and measures of specific cognitive domains, including testing of executive function (Raven's Progressive Matrices, Stroop test, Wisconsin Card Sorting Test), attention (Trail Making Test, versions A and B), memory (Rey Test, Long-Term Memory, Working Memory, Visuo-Spatial Memory), and language (Phonemic fluency and Category fluency). Raw scores were corrected for age and years of education using normative data available for each test and converted to *z*-scores. *Z*-scores ≤ -1.5 were considered indicative of test impairment. ET patients whose test results did not reveal any impairment or impairment in only one test were classified as having normal cognition (ET-NC). ET patients whose test results revealed an impairment in at least half of the tests in one domain or impairment in at least half of the tests in ≥ 2 domains were considered as having single or multi-domain

mild cognitive impairment (MCI), respectively. ET-MCI was subdivided into subtypes including amnestic single-domain (a-MCI), amnestic multi-domain (a-MCI+), non-amnestic single-domain (na-MCI), or non-amnestic multi-domain (na-MCI+). Two impaired executive function tests were required for a patient's executive function domain to be considered impaired, while only one impaired test was required for all the other domains [6].

Psychiatric Assessment

The psychiatric assessment was designed specifically for the study by a trained psychiatrist and was based on the structured clinical interview for DSM-IV criteria using the structured Clinical Interview (SCID-I) for axis I disorders and the SCID-II for axis II disorders [5, 23]. Axis I includes psychotic, depressive, anxiety, somatoform, dissociative, and adjustment disorders, except for the personality disorders and mental retardation, which are reported on axis II. The psychiatric assessment included the Hamilton Depression Rating Scale (HAM-D), the Hamilton Anxiety Rating Scale (HAM-A), the Brief Psychiatric Rating Scale (BPRS), and the Clinical Global Impression-Severity scale (CGI-S) [5].

Statistical Analysis

Categorical variables were summarized as frequencies and compared by using Yates' chi-square test. Numerical data were expressed as mean values ±1 standard deviation (SD), unless otherwise specified, and compared by using the Mann-Whitney *U* test. The possible relationship between kinematic data of postural and kinetic tremor was assessed by Spearman's rank correlation coefficient. Logistic regression was used to identify whether the presence of head tremor (dependent variable) was associated with a more severe tremor of the upper limbs and the presence of cognitive and psychiatric symptoms (independent variables). Age- and gender-adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were reported. All statistical analyses were performed using the statistical software R version 3.5.1. The statistical significance threshold was set at $P \leq 0.05$. The false discovery rate correction was applied to multiple comparisons [24].

Results

Demographic Data

The patients' mean age ± 1SD was 68.6 ± 11.7 years (range, 20–82). The mean disease duration ± 1 SD was 13.51 ± 13.87 years. The mean age at onset ± 1SD was 55.3 ± 17.4 years. A positive family history was present in 37/70 cases (52.8%). Twenty-one patients (30.0%) had tremor of the upper limbs plus head tremor. ET patients with head tremor were older than ET patients without head tremor (73.9 ± 7.1 vs. 66.3 ± 12.7, $P < 0.01$); however, the two groups did not differ in terms of disease duration (14.5 ± 13.6 vs. 13.0 ± 14.2, $P = 0.40$). Finally, there were no gender-ratio differences between patients with and without head tremor (9 females/12 males vs. 32 females/16 males, $P = 0.11$).

Tremor Data

The FTMTRS total score ± 1 SD, in the overall sample of ET patients was 18.27 ± 12.43 and it was slightly higher in patients with upper limb tremor plus head tremor in comparison with those with upper limb tremor alone (18.13 ± 12.29 vs. 16.22 ± 10.31; $P = 0.06$; Table 1); a difference between these two groups was highly significant when comparing the FTMTRS part A sub-score (8.42 ± 4.61 vs. 5.71 ± 3.17; $P < 0.001$; Table 1).

The analysis of postural tremor indicates that magnitude (whole sample GRMS^2, 0.60 ± 0.32) and frequencies (whole sample Hz, 7.04 ± 1.07) were similar in all the ET patients classified according to body distribution (both $Ps > 0.05$; Tables 1, 2, and 3). The analysis on kinematic variables of upper limb tremor during the "pointing task" (whole sample average values ± 1 SD for number of movements, 8.93 ± 3.30; distance, 0.47 ± 0.15; velocity peak, 1.38 ± 0.81; acceleration peak, 13.18 ± 6.15; D/A acceleration, 0.63 ± 0.29; and CI, 1.06 ± 0.06) revealed a significant difference in the CI, i.e., more severe kinetic tremor in ET with upper limb tremor plus

Table 1 Tremor data in ET patients classified for tremor distribution

	ET UL (49)	ET UL + H (21)	*P*
Tremor clinical data scores			
FTMRS total score	16.22 ± 10.31	18.13 ± 12.29	0.06
FTMRS part A	*5.71 ± 3.17*	*8.42 ± 4.61*	*< 0.01*
FTMRS part B	6.92 ± 5.19	8.81 ± 7.15	0.35
FTMRS part C	3.63 ± 3.47	5.81 ± 4.83	0.08
Tremor kinematics			
GRMS^2	0.61 ± 0.36	0.59 ± 0.31	0.76
Hz	7.02 ± 0.89	6.95 ± 1.28	0.53
No. mov.	*9.50 ± 3.27*	*8.86 ± 3.32*	*0.02*
Distance (m)	0.46 ± 0.15	0.46 ± 0.14	0.65
Vel. peak (m/s)	1.36 ± 0.54	1.36 ± 0.80	0.18
Acc. peak (m/s^2)	13.79 ± 6.00	13.09 ± 6.11	0.16
D/A	0.58 ± 0.15	0.72 ± 0.45	0.92
CI	*1.05 ± 0.03*	*1.08 ± 0.09*	*< 0.01*

Significant values and *P* values are in italics. *UL*, upper limb; *H*, head; *FTMRS*, Fahn Tolosa Marin Rating Scale; *No. mov*, number of movements; *Vel. peak*, velocity peak; *Acc. peak*, acceleration peak; *D/A*, deceleration/acceleration ratio; *CI*, curvature index

Table 2 Cognitive data in ET patients classified for tremor distribution

	ET UL (49)	ET UL + H (21)	*P*
MMSE	27.88 ± 0.94	27.57 ± 1.13	0.14
MCI	15/49 (30.6%)	8/21 (38%)	0.74
a-MCI	1/49 (2%)	0/21 (0%)	0.39
a-MCI+	9/49 (18.36%)	7/21 (33.3%)	0.29
na-MCI	2/49 (4%)	0/21 (0%)	0.22
na-MCI+	3/49 (7.7%)	1/21 (4.8%)	1

UL, upper limb; *H*, head; *MMSE*, Mini-Mental State Examination; *MCI*, mild cognitive impairment; *a-MCI*, amnestic single-domain MCI; *a-MCI+*, amnestic multi-domain MCI; *na-MCI*, non-amnestic single-domain MCI; *na-MCI+*, non-amnestic multi-domain MCI; *HAM-D*, Hamilton Depression Rating Scale; *HAM-A*, Hamilton Anxiety Rating Scale; *BPRS*, Brief Psychiatric Rating Scale; *CGI-S*, Clinical Global Impression-Severity Scale

head tremor in comparison with those upper limb tremor alone (1.08 ± 0.09 vs. 1.05 ± 0.03; $P < 0.01$; Table 1). No significant between-group differences emerged for the other movement parameters during the pointing task (all $Ps > 0.05$; Table 1). Spearman's rank correlation coefficients analysis showed no relationship between kinematic data of postural and kinetic tremor (all $Ps > 0.05$); thus, trajectory measure (CI) and other kinematic parameters during the pointing task could not simply be interpreted as a compensatory phenomenon in response to increased postural tremor (Table 1).

Cognitive Data

The neuropsychological tests showed an average MMSE score of 27.79 ± 1.00. The cognition was normal in 47 (67.1%) patients, while 23 (32.8%) had ET-MCI: a-MCI+ was the most common (16/23; 69.5%) form of ET-MCI, followed by na-MCI+ (4/23; 17.4%), na-MCI (2/23; 8.7%), and a-MCI (1/23; 4.3%). No cognitive differences were detected in ET patients with and without head tremor (all $Ps > 0.05$; Table 2).

Table 3 Psychiatric data in ET patients classified for tremor distribution

	ET UL (49)	ET UL + H (21)	*P*
Axis I	*18/49 (36.7%)*	*16/21 (76.2%)*	*< 0.01*
Axis II	5/49 (10.2%)	1/21 (4.76%)	0.98
Ham-D	6.79 ± 6.21	7.27 ± 6.71	0.51
Ham-A	8.26 ± 6.50	8.13 ± 6.38	0.82
BPRS	28.91 ± 4.61	28.68 ± 5.31	0.74
CGI-S	1.24 ± 1.25	1.27 ± 1.22	0.79

Significant values and *P* values are in italics. *UL*, upper limb; *H*, head; *HAM-D*, Hamilton Depression Rating Scale; *HAM-A*, Hamilton Anxiety Rating Scale; *BPRS*, Brief Psychiatric Rating Scale; *CGI-S*, Clinical Global Impression-Severity Scale

Psychiatric Data

The SCID-I showed that axis I psychiatric disorders were present in 34 out of 70 (48.5%) ET patients. Eleven of them (15.7%) presented a generalized anxiety disorder, 7 (10%) a major depressive disorder, 7 (10.0%) an adjustment disorder, 3 (4.0%) a panic disorder, 3 (4.0%) social phobia, 2 (2.8%) dysthymic disorders, and 1 (1.4%) an anxiety disorder NOS. The SCID-II showed that axis II psychiatric disorders, i.e., personality disorders, were present in 6 of the 70 (8.5%) ET patients. Other results of the psychiatric assessment on the whole sample of ET patients were HAM-D, 7.30 ± 6.81; HAM-A, 7.70 ± 6.64; BPRS, 29.02 ± 4.53; and the CGI-S, 1.27 ± 1.21. Interestingly, the occurrence of axis I psychiatric disorders was higher in ET patients with upper limb tremor plus head tremor than in those with upper limb tremor alone (76.2% vs. 36.7%; $P < 0.01$; Table 1, Fig. 1); by contrast, the SCID-II showed that the occurrence of axis II psychiatric disorders, i.e., personality disorders, was comparable in patients with ET with and without head tremor (4.76% vs.10.2%; $P = 0.98$; Table 3). Finally, there was no significant difference for Ham-D, Ham-A, BPRS, and CGI-S scores between the two groups (all $Ps > 0.05$; Table 3). No differences in tremor severity, as assessed by FTMTRS, were found between patients with and without axis I psychiatric disorders (18.29 ± 9.8 vs 18.25 ± 14.63, $P = 0.98$).

Logistic Regression Analysis

The logistic regression analysis identified "tremor distribution" as being associated with a higher risk of axis I psychiatric disorders (OR, 5.5; 95% CI, 1.80–19.20; $P = 0.004$) and with a lower number of movements during the pointing task (OR, 0.89; 95% CI, 0.67–0.97; $P = 0.03$). There was also a trend toward an association between "tremor distribution" and higher CI values (OR, 1.14; 95% CI, 1.02–1.34; $P = 0.06$). By contrast, there were no significant associations between tremor characteristics and other tremor features or cognitive and psychiatric abnormalities and there was no significant effect of the covariate age and gender (all $Ps > 0.05$).

Discussion

We here observed that approximately 1/3 of the ET patients in our sample had upper limb tremor plus head tremor. The novel finding is that clinical and neurophysiological features of ET patients vary in those with and without head tremor. Specifically, kinematic analysis showed that kinetic tremor of the upper limbs was more severe in ET patients with head tremor than in those with upper limb tremor alone. Similarly, in ET patients with head tremor, the occurrence of psychiatric (axis I) disorders was higher in comparison with patients with

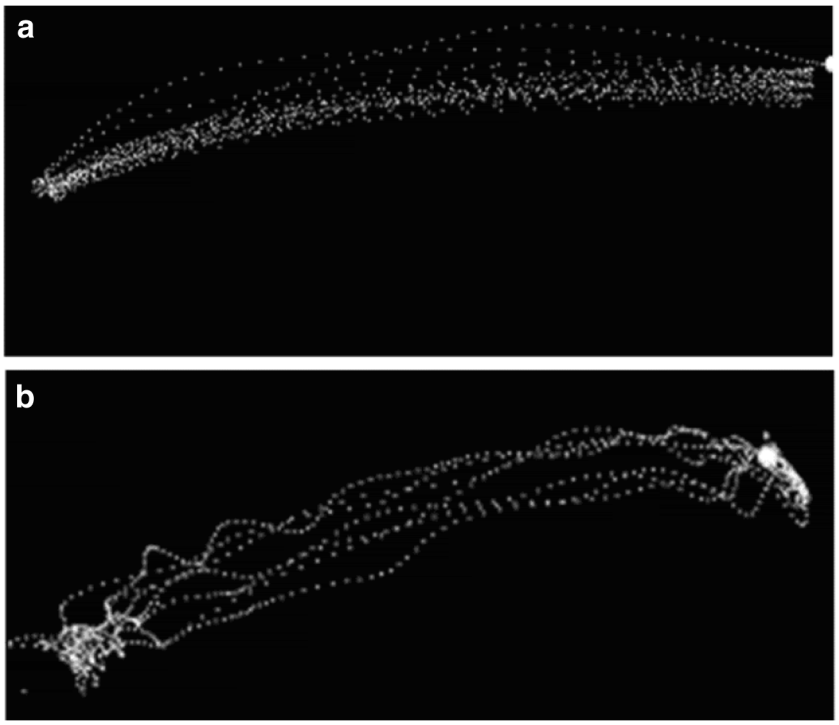

Fig. 1 Arm movement trajectories during the "pointing task" in two representative ET patients: without head tremor (upper panel) (**a**) and with head tremor (lower panel) (**b**). Note that the movement trajectories in ET patients with head tremor had altered profile (i.e., a higher curvature index, CI) in comparison with ET patients without head tremor

upper limb tremor only. Tremor distribution did not, instead, affect the occurrence of cognitive changes in patients. These findings support the notion that the presence of head tremor significantly influences the variable clinical presentation of ET.

We designed our study to ensure that methodological aspects did not bias the results. Indeed, since all the patients had discontinued any therapy at least 48 h prior to the clinical and neurophysiological assessment, a possible confounding effect of medication is unlikely. Moreover, as patients were consecutively recruited, we rule out any selection bias. Although the diagnosis of ET still relies on clinical criteria, the patients included in the study had been followed up in our outpatient clinic for a relatively long period prior to enrollment in the study, thus minimizing the risk of misdiagnosis. All the ET patients had typical postural and kinetic tremor of the upper limbs with subsequent involvements of the head and none had any other prominent neurological features suggestive of different neurological conditions including bradykinesia, dystonic posturing, or ataxia nor signs of systemic illness [3].

The first original finding yielded by our neurophysiological analysis is that kinetic tremor in the upper limbs, as revealed by altered trajectories during arm movements and higher CI values [18, 20, 22], was more severe in ET with head tremor than in those with upper limb tremor alone. Because altered trajectories during arm movements are thought to reflect a cerebellar dysfunction [12, 25], our results can be then interpreted as a further indirect evidence of the more severe involvement of cerebellum in ET affecting both arm and head. Our hypothesis is supported by neuroimaging data showing varying degrees of cerebellar gray matter atrophy in ET patients with head tremor and in those without head tremor [8], with more severe atrophy of the cerebellar vermis being detected in ET patients with head tremor. More recently, Dyke et al. confirmed a marked gray matter reduction across multiple cerebellar regions in ET patients with head tremor, as shown by a lobule by lobule analysis [9]. Finally, pathological evidence also indicates that ET patients with head tremor had more Purkinje cell axonal swellings with torpedo formation in the cerebellar vermis [10]. ET in patients with upper limb tremor plus head tremor may be a more severe subtype compared with ET in patients with upper limb tremor only. Supporting this hypothesis, the FTMTRS total score was slightly higher in patients with upper limb plus head tremor in comparison with that in patients with upper limb tremor only. The difference between the two groups was even more evident when comparing the FTMTRS part A sub-score, which specifically represents tremor severity as reported by the examiner.

In the present study, we found axis I psychiatric disorders in 48.5% ET patients and axis II psychiatric disorders in 8.5% ET patients. These results are similar to those reported by Fabbrini et al. [5], who found axis I disorders in 54% and axis II psychiatric disorders in 13.5% of ET patients. The novel observation of our study is that the occurrence of axis I psychiatric disorders was higher in ET patients with upper limb tremor plus head tremor than in those with upper limb tremor alone. This finding may be explained by a predominant involvement of the cerebellum in the pathophysiology of these ET patients. The cerebellum, especially the vermis [26], is

reciprocally connected with the limbic system and is known to alter affective processes [27–29]. Functional neuroanatomic data [28, 30–32] as well as evidence from neuroimaging studies [33–35] have recently underlined the role of cerebellum in neuropsychiatric disorders. The presence of a higher occurrence of psychiatric disorders in patients with upper limb plus head tremor may alternatively reflect the disease burden, due to the higher severity of ET in this subgroup of patients. However, because we found no difference in FTMTRS scores between patients with and without axis I psychiatric disorders, we consider this hypothesis unlikely. The fact that head tremor in ET was found to be the factor contributing most to the presence of axis I psychiatric disorders may thus suggest that psychiatric disorders should be considered as a specific manifestation of ET itself [5].

The results that emerge from the neuropsychological testing performed in our study agree with those from previous studies that documented cognitive impairment in ET [36, 37]. Indeed, we found that 32.8% of ET patients had MCI and that a-MCI+ was the most common subtype. Several putative mechanisms have been proposed for the mechanisms underlying cognitive impairment in ET, which has yet to be fully understood. In this regard, cognitive abnormalities in ET have been hypothesized to result from a network dysfunction that includes cerebellar, thalamic and frontal areas [6, 38, 39]. Confirming earlier observations by Collins et al. [6] our results indicate that cognitive changes in ET are not clearly related to tremor characteristics (body distribution). Thus, we may conclude that complex interactions between various clinical factors (possibly including family history, disease duration, and age of onset) and aging, contribute to the presence of cognitive changes in ET. Along with previous observations [6], the results of the present study possibly indicate, however, that cognitive abnormalities in ET should be considered as a comorbidity rather than as a manifestation of the disease itself.

This study has several limitations that should be mentioned. Firstly, the study sample is relatively limited, and therefore, we focused our analysis on head tremor as the major determinant of the variable clinical presentation of ET. Further investigations on larger samples should also focus on familial vs. sporadic forms as well as on patients with varying disease duration and age at onset, to see whether all these possible sources of variability also influence the clinical presentation of ET. In our study, we did not consider these factors considering the relatively low level of genotype/phenotype correspondence, which has also been reported in other conditions, and the lack of well-defined cut-offs reflecting the biological and pathogenic mechanism underlying ET. Although the study sample is relatively small, this is, to our knowledge, the largest systematic assessment of tremor including kinematic techniques and of cognitive and psychiatric symptoms in ET patients that has been performed to date. Secondly, we did not assess ET with and without head tremor by means of neuroimaging techniques as this was beyond the scope of our study. Our findings thus warrant experimental confirmation based on these techniques.

In conclusion, this is the first study that has systematically examined the association between head tremor and various symptoms in ET patients. Moreover, we assessed tremor and cognitive and psychiatric symptoms in the same patients. The results indicate that head involvement influence tremor severity and psychiatric symptoms in ET, whereas head tremor involvement appears to play a less important role for cognitive symptoms in this condition. These data support the notion that head tremor may represent a distinct ET subtype characterized by a prominent cerebellar involvement and that psychiatric disorders should be considered as a specific manifestation of ET itself. The data highlights the importance of the evaluation of psychiatric disorders in ET, particularly in patients with head tremor.

Compliance with Ethical Standards

The local institutional review board approved the experimental procedures and all the participants gave their written informed consent to the study. Authorization has been obtained for disclosure of any recognizable persons in videos. The experiments adhered to the regulations laid down in the Declaration of Helsinki.

Conflict of Interest The authors declare that they have no conflicts of interest.

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