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ORIGINAL ARTICLE

A comparison between rate of nonmotor symptom development in essential tremor and Parkinson's disease

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Abstract In the last decade our perspective on essential tremor (ET) as a pure motor system disorder has begun to change. By virtue of recent studies of nonmotor symptoms (NMSs) that are used to characterize Parkinson's disease (PD), these symptoms have also been added to the definition of ET. There is increasing evidence to suggest that ET might not be as benign and monosymptomatic as we previously thought. The aim of this study was to evaluate nonmotor symptoms in ET, and to compare them with PD. We studied 37 ET and 23 PD patients. Tremor rate was evaluated using the Fahn–Tolosa–Marin tremor rating scale (FTM-TRS) in ET patients. The patients with PD were scored for motor symptoms using the unified Parkinson's disease rating scale (UPDRS)-III and the Hoehn–Yahr scale. Cognitive functions were assessed with the Montreal Cognitive Assessment (MoCA) test. NMSs were evaluated with the nonmotor symptoms questionnaire (NMSQuest). In the ET group, the most common NMSs were forgetting things, feeling sad, nocturia, urgency, and difficulty concentrating. The mean NMSQuest score was 8.43 ± 4.14 in the ET group and 14.06 ± 5.44 in the PD group (p value <0.001). However, except for 12 items in NMSQuest, in comparing items one by one there was no statistical difference between them. The mean MoCA total score was 17.81 ± 4.56 in the ET group and 17.08 ± 4.08 in the PD group (p value 0.675). There were no significant differences in MoCA subgroup scores. Evaluation of nonmotor symptoms in ET may help us to understand this emerging definition of ET. This study contributes evidence toward this new concept.

Keywords Essential tremor · Parkinson's disease · Nonmotor symptom · Cognitive function

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Introduction

Essential tremor (ET) is known as a benign, monosymptomatic, pure motor tremor disorder. This understanding is changing. There is increasing evidence to suggest that the disease might be more heterogeneous than previously thought. Anatomic and pathologic studies, progression of the disease over time and absence of remission make us think that ET could be a neurodegenerative disease [1]. Lewy body (LB) pathology, Purkinje cell (PC) loss with torpedoes and Bergman gliosis were found in recent autopsy studies. These findings also corroborate the neurodegenerative theory [2]. Lately, some new clinical, neuroimaging and electrophysiological studies indicate that ET can be considered as a progressive disease and is associated with subtle neurological deficits including bradykinesia (mild), cerebellar dysfunction (abnormal eye blink reflex conditioning, deficits in paced finger typing, dysfunction in hand–eye coordination and ocular

movements, mirror movements, mild dysarthria, tandem gait ataxia, olfactory and hearing loss and nonmotor features such as mild cognitive deficits, neuropsychiatric symptoms (anxiety, depression, specific personality traits), sleep disorders, and decreased body mass index [3, 4]. Despite all this, it is argued by some researchers that the evidence is not sufficient to classify ET as a neurodegenerative disease. Disputes about ET as a neurodegenerative disease are still ongoing [5–7].

Associations with neurological or neurodegenerative disorders (Parkinson's disease, dystonia, myoclonus, possibly associated with migraine, restless leg syndrome, LB dementia and Alzheimer disease) have been studied [4]. The relation with Parkinson's disease (PD) is the most well known. There are some shared motor symptoms with Parkinson's disease (PD), including resting tremor, bradykinesia, postural instability and cognitive deficits [8]. The predisposition to develop PD in some ET cases indicates a relationship between ET and PD. In some cases, PD overlaps with the presentation of ET—so-called "ETPD" cases [9, 10].

PD is a progressive neurodegenerative disorder that is known to be associated with NMSs including neuropsychiatric symptoms (depression, apathy, anxiety, hallucinations, dementia, confusion, delirium), sleep disorders (restless leg syndrome, excessive daytime sleepiness, frightening dreams, REM sleep behavior disorder), autonomous symptoms (sialorrhea, sexual dysfunction, xerostomia), gastrointestinal symptoms (constipation, nausea, fecal incontinence), and sensorial symptoms (pain, paresthesia). These symptoms are important clinical issues for patients and quite easily missed by clinicians unless they are asked about [11].

ET is increasingly known for several nonmotor symptoms as in PD [12, 13]. Recent studies mostly researched the mild cognitive deficits and neuropsychiatric conditions (personality traits, mood disorders, anxiety disorders) [14–16]. The aim of this study was to compare cognitive functions and nonmotor symptoms of ET with PD.

Methods

120 patients with tremor (aged 45–84) who applied to our outpatient unit of the Neurology Department between November 2012 and December 2013 were enrolled in the study. We ruled out other possible causes of tremor and pseudodementia (low or high serum thyroid hormone levels, low vitamin B12 levels, hemogram and other biochemical blood tests such as liver and kidney functions). Other exclusion criteria were known neuropsychiatric disorder (depression, which can affect cognitive functions, anxiety disorder, dementia, restless leg syndrome, sleep disorders, etc.), neurological or psychiatric medication use (except medication for tremor) or medication use that can cause tremor (asthma medicines such as theophylline and albuterol, stimulants such as amphetamines, heart medicines such as amiodarone, procainamide, thyroid medication such as levo thyroxine, cancer medicines such as thalidomide and cytarabin, seizure medicines such as valproic acid) or affect cognitive functions (such as antiepileptic agents, antidepressants, etc.), disorders of the prostate, diabetes mellitus, any kind of cancer, tremor less than 6 months, declining to participate, and other reasons such as being illiterate and intellectual disability.

Ours is a countryside area where people have a low level of education and are occupied with agriculture. An important part of the patients were illiterate and thus these individuals were excluded from the study. 37 patients with ET and 23 patients with PD were recruited for the study. All patients were interviewed for socio-demographic characteristics and clinical history, ET patients according to the diagnostic criteria of ET by Bain et al. and PD patients according to the United Kingdom PD Brain Bank (UKPDBB) criteria, being established by two neurologists [17, 18]. Tremor rate was evaluated using the Fahn–Tolosa–Marin Tremor Rating Scale (FTM-TRS) by the same neurologists [19]. Motor symptoms of PD patients were scored using the Unified Parkinson's Disease Rating Scale-III (UPDRS-III). Staging was performed using the Hoehn–Yahr scale. Cognitive functions were evaluated using the Turkish version of the MoCA test by a neuropsychologist. The MoCA test is a rapid screening test for assessing mild cognitive deficit. Subgroups of the test are visuospatial/executive functions, naming, memory, attention, language, abstraction, delayed recall and orientation. The maximum score is 30; a score of 21 or above is considered as normal in the Turkish version [20–22]. All patients answered the nonmotor symptoms questionnaire (NMSQest), which is a 30-item self-administered questionnaire evaluating NMSs [23–26].

The study protocol was conducted in accordance with the ethical principles stated in the 'Declaration of Helsinki' and approved by the Ethical Committee of Erzurum Regional Training and Research Hospital. Informed consent of the participants was obtained after the nature of the procedures had been fully explained.

SPSS 17.0 was used for the analysis. The definitive statistics in the study were summarized with the use of arithmetic means, mean standard deviation, etc. Numbers and percentages were used in the representation of categorical variables. The Mann–Whitney U test was utilized for representation of numeric data regarding the comparison of control and patient groups, under the assumption that the data was not distributed normally. The comparisons for categorical variables were represented and

analyzed by cross tabulation (Chi-square). Fisher's exact test was used to compare the frequency of NMS between the PD and ET groups. For correlations we used Pearson's correlation analysis. A statistical significance limit of $p < 0.05$ was used.

Results

37 ET patients and 23 PD patients were evaluated. The mean age was 62.02 ± 8.10 (ranked 45–80) in the ET group and 66.21 ± 9.48 (ranked 48–84) in the PD group (p value 0.073). Both groups had similar socio-demographic attributes (age, gender, education level, employment). Table 1 shows the demographic characteristics.

The mean duration of the disease was 7.23 ± 9.38 in the ET group and 5.15 ± 4.29 in the PD group (p value 0.329).The mean FTM-TRS score was 19.05 ± 12.29 in the ET group. The mean Hoehn–Yahr scale score was 1.78 ± 0.79 and the UPDRS-III score was 15.47 ± 7.94 in the PD group.

The mean MoCA total score was 17.81 ± 4.56 in the ET group and 17.08 ± 4.08 in the PD group (p value 0.675). MoCA subgroup scores were not significantly different between each group. Table 2 shows the comparison of MoCA subgroup scores.

The mean NMSQest score was 8.43 ± 4.14 in the ET group and 14.06 ± 5.44 in the PD group (p value <0.001). When we compared the rate of the different items one by one, there was no statistically significant difference for the 18 items. Table 3 shows a comparison of the rate of NMSs in both groups.

In the ET group, the most common nonmotor symptoms were forgetting things, feeling sad or blue, nocturia, urgency, and difficulty concentrating. In the PD group, forgetting things, nocturia, urgency, constipation, feeling sad or blue, pain, and difficulty concentrating were the most common nonmotor symptoms.

There was a positive correlation between UPDRS and NMSQuest mean scores ($r = 0.70$, p value <0.001) and a negative correlation between UPDRS and MoCA total scores ($r = -0.493$, p value 0.017). But there was no correlation between FTM-TRS and MoCA total scores ($r = 0.082$, p value 0.629) or NMSQuest mean scores ($r = 0.105$, p value 0.536).

Table 1 Socio-demographic characteristics

	ET patients ($n = 37$)	PD patients ($n = 28$)	p value
Age (years)	62.02 ± 8.10	66.21 ± 9.48	0.073
Gender			0.098
Male	16 (43.2 %)	15 (65.2 %)	
Female	21 (56.8 %)	8 (34.8 %)	
Employment			0.991
Employee	8 (21.6 %)	29 (78.4 %)	
Unemployed, homemaker, retired	5 (21.7 %)	18 (78.3 %)	
Education level			0.563
Elementary school	28 (75.7 %)	20 (87.0 %)	
Secondary school	5 (13.5 %)	1 (4.3 %)	
High school	3 (8.1 %)	2 (8.7 %)	
University	1 (2.7 %)	0 (0.0 %)	

Table 2 MoCA total scores and subgroup scores means

	ET patients ($n = 37$)	PD patients ($n = 23$)	p value*
MoCA total score	17.81 ± 4.56	17.08 ± 4.08	0.675
Subgroups			
Visuospatial/executive	1.83 ± 1.19	2.69 ± 3.03	0.183
Naming	2.0.2 ± 0.64	2.13 ± 0.81	0.545
Attention	4.43 ± 1.67	4.39 ± 1.46	0.649
Language	1.27 ± 0.96	0.95 ± 0.76	0.209
Abstraction	0.97 ± 0.76	1.00 ± 0.73	0.890
Delayed recall	1.45 ± 1.42	1.04 ± 1.06	0.343
Orientation	5.59 ± 0.89	5.47 ± 0.84	0.398

* Mann–Whitney U test

Discussion

The main subject of this study was to determine the rate of nonmotor symptom development in ET and to compare it with PD. We applied the MoCA test for assessing mild cognitive deficits and NMSQuest to evaluate NMSs. When we compared the MoCA total score and subgroup score means between ET and PD patients, there was no significant difference. The rate of NMSs was higher in the PD group than the ET group but in comparing the rate of 18 individual items there were no statistically significant differences. That is to say 12 items were more specific to PD but the others had a similar rate in ET. Forgetting things, feeling sad or blue, and nocturia were the most common NMSs in ET patients. The result of this study was that the cognitive deficit in ET and PD was similar. Beyond the characteristic motor signs, ET has many nonmotor features. These were not as common as in PD but were noteworthy.

One of the first studies about cognitive function in ET belongs to Gasparini et al. Their study showed that the frontal lobe feature of ET was similar to that of PD, as we also found [27]. Lombardi and colleagues studied a small group of ET and they found that patients with ET have deficits in tests of verbal fluency, naming, mental set-shifting, verbal memory and working memory [28].

Table 3 Comparison the rate of NMSs in both group

NMSs	ET patients ($n = 37$) (%)	PD patients ($n = 23$) (%)	p value*
Hypersalivation	7 (18.9)	6 (16.1)	0.535
Loss/change taste or smell	8 (21.6)	13 (56.5)	**0.011**
Difficulty swallowing	10 (27.0)	10 (43.5)	0.261
Nausea	7 (18.9)	9 (39.1)	0.133
Constipation	14 (37.8)	17(73.9)	**0.009**
Fecal incontinence	0 (0.0)	0 (0.0)	–
Incomplete bowel emptying	8 (21.6)	16 (69.6)	**<0.001**
Urgency	21 (67.6)	17 (73.9)	0.271
Nocturia	25 (67.6)	19 (82.6)	0.242
Unexplained pains	13 (35.1)	17 (73.9)	**0.007**
Unexplained change in weight	3 (8.1)	7 (30.4)	**0.035**
Problems remembering things/forgetfulness	28 (75.7)	20 (87.0)	0.340
Loss of interest	16 (43.2)	13 (56.5)	0.427
Hallucinations	2 (5.4)	7 (30.4)	**0.021**
Difficulty concentrating or staying focused	19 (51.4)	17 (73.9)	0.108
Feeling sad or blue	26 (70.3)	17 (73.9)	1.000
Feeling anxious, frightened or panicky	13 (35.1)	11 (47.8)	0.419
Feeling less/more interested in sex	10 (27.0)	9 (39.1)	0.397
Finding it difficult to have sex when you try	3 (8.1)	4 (17.4)	0.412
Dizziness	15 (40.5)	13 (56.5)	0.291
Falling	3 (8.1)	10 (43.5)	**0.003**
Excessive daytime sleepiness	15 (40.5)	16 (69.6)	**0.036**
Insomnia	19 (51.4)	16 (69.6)	0.189
Intense, vivid or frightening dreams	4 (10.8)	9 (39.1)	**0.021**
Talking or moving in your dreams/acting out during a dream	5 (13.5)	12 (52.2)	**0.003**
Unpleasant sensation in legs	6 (16.2)	7 (30.4)	0.215
Swelling of the legs	3 (8.1)	10 (43.5)	**0.003**
Excessive sweating	8 (21.6)	10 (43.5)	0.089
Double vision	0 (0.0)	4 (17.4)	**0.018**
Delusions	0 (0.0)	2 (3.3)	0.143

Bold values represent significant difference between ET and PD patients

* Fisher' s exact test

Lacritz et al. observed dysfunction of frontal-mediated processes [29]. Tröster et al. and Sahin et al. concluded that subclinical cognitive deficits characterized by visuospatial, verbal memory impairments and executive functions might be a clinical feature of ET and the cerebello-thalamo-frontal network might play a role in the pathophysiology of ET [30, 31]. Benito-León observed that a fronto subcortical-type dysfunction occurred in some ET patients and that lower cognitive test scores in ET, rather than being clinically inconsequential, seem to have a clinical–functional correlate [32]. Louis and colleagues found an association between lower cognitive test scores and functional difficulty [33]. Kim et al. also found an association between tremor severity and cognitive impairment. In our study, we failed to find any correlation between tremor severity and cognitive function [34]. Bermajo-Pareja et al. suggested that ET was associated with increased risk of dementia [35].

If we summarize the topic: research into cognitive deficits in ET have shown that ET patients have deficits of attention (verbal, auditory and visual), concentration, working memory, executive functions, verbal memory, verbal fluency, mental processing speed, and visuospatial function, which are due to cortical–subcortical–cerebellar loop dysfunction [4]. We observed deficits of visuospatial/executive functions, naming, memory, attention, language, abstraction, delayed recall and orientation in our ET patients.

The main goal of this study was to evaluate the rate of NMSs in ET. 18 items had a similar rate as in PD. The mean NMSQest score was 8.43 ± 4.14 in the ET group and 14.06 ± 5.44 in the PD group (p value <0.001). Giorelli et al. did not find a significant difference in the total number of NMS reported by either PD (10.4 ± 4.9) or ET patients (8.41 ± 3.3) [36]. Sarah and her colleagues reported 10.4 ± 3.4 in PD patients and 6.1 ± 2.4 in ET patients [37]. The rate of development of NMSs in our ET patients was more similar to Giorelli's study, but the mean NMSQuest score in our PD group was higher and we found a significant difference between ET and PD.

The symptoms which were more specific to PD were: loss/change of taste or smell (56.5 %, p value 0.011), constipation (73.9 %, p value 0.009), incomplete bowel emptying (69.6 %, p value <0.001), unexplained pains (73.9 %, p value 0.007), unexplained change in weight (30.4 %, p value 0.035), hallucinations (30.4 %, p value 0.021), falling (43.5 %, p value 0.003), excessive daytime sleepiness (69.6 %, p value 0.036), intense, vivid or frightening dreams (39.1 %, p value 0.021), talking or moving in dreams/acting out during a dream (52.2 %, p value 0.003), swelling of legs (43.5 %, p value 0.003), and double vision (17.4 %, p value 0.018). Giorelli et al. observed that PD patients reported more drooling (29 %), hyposmia (32.2 %), hallucinations (19.3 %), difficulty in concentrating (51.6 %), orthostatic dizziness (67.7 %), falling (19.3 %), vivid dreams (32.2 %), REM sleep behavior disorder (58 %), and diplopia (22.5 %) compared with ET patients [36]. These findings are similar to our study.

In the ET group, the most common NMS was forgetting things. Benito-León and colleagues also observed that the

complaint of forgetfulness was common in ET [32]. Feeling sad or blue was the second common NMS in the ET group. Lombardi et al. [28] found higher levels of depressive symptoms in patients with ET. Louis and colleagues' study showed that there was a significant association between ET and depression and a significant risk of developing ET in patients with self-reported depression [38]. Nocturia was the third most common condition in the ET group. In Giorelli's follow-up study, the most common NMSs in ET were orthostatic dizziness (67.7 %), anxiety (64.5 %), and nocturia (61.2 %) [39]. The percentage of the patients who had nocturia was 67.6 % in our ET group. These rates are quite similar to each other.

There were some limitations of this study, such as that we did not ask about smoking habits or alcohol use. The study group was small. Cognitive assessment was limited to the MoCA test. Our patients had a low level of education.

Asking patients about NMSs by using NMSQuest, evaluation of NMSs belonging to various systems, and evaluation of cognitive functions with a test that was easy to apply and comparing with PD were the strong parts of our study.

Studies with long-term follow-up and large sample size are needed for understanding whether ET is a neurodegenerative syndrome characterized by a number of motor and nonmotor features rather than a monosymptomatic system disorder, or whether ET cases that have NMSs could be those who will develop PD in the future. Evaluation of NMSs in ET may help us to understand this emerging definition of ET. This study contributes some evidence to this new concept.

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Conflict of interest The authors declare that there is no conflict of interest.

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