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ORIGINAL ARTICLE

Cognitive functions, fatigue, depression, anxiety, and sleep disturbances: assessment of nonmotor features in young patients with essential tremor

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Abstract There is a growing amount of evidence to suggest that besides motor features, patients with essential tremor (ET) may exhibit significant nonmotor features, such as mild cognitive deficits, fatigue, neuropsychiatric symptoms, and sleep disturbances. The goal of this study was to examine nonmotor features in young patients with ET and their impact on quality of life. 45 patients (24.55 ± 7.16 years old) with ET and 35 controls were evaluated using the Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, Beck Depression Inventory, Beck Anxiety Scale, Fatigue Severity Scale, and Short Form-36. Cognitive functions were evaluated using the Turkish version of the Montreal Cognitive Assessment Battery (MoCA). We ruled out other possible causes of the tremor. The tremor rate was evaluated using the Fahn–Tolosa–Marin Tremor Rating Scale. Poor sleep quality, fatigue, anxiety, and depressive symptoms were more common, and MoCA total scores were lower in the patient group. Fatigue, depressive symptoms, and higher anxiety levels were seen to have a negative effect on physical and mental health. Excessive daytime sleepiness had a negative effect on physical health. There is an emerging interest in nonmotor features of ET. This study showed that even young patients have nonmotor features that decrease their quality of life. This might tell us that nonmotor symptoms could be a part of the disease in the early stages.

Keywords Essential tremor · Nonmotor feature · Mild cognitive deficit · Sleep quality · Fatigue

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Introduction

Essential tremor (ET) is one of the most common movement disorders that neurologists confront in daily clinical practice [1]. In a population-based study in Turkey, the prevalence of ET was found to be 4 % among individuals aged 40 years or older [2]. In another study performed door to door in the center of the city of Erzurum, the prevalence of ET among individuals aged between 18 and 60 was found to be 1.60 % [3].

ET is known as a monosymptomatic, slowly progressing, benign, pure motor system disease characterized by an 8–12 Hz kinetic tremor that occurs during voluntary movements. This definition of ET has been questioned in the last decade. In light of recent studies, the disease seems to be more heterogeneous than we thought. It includes motor features such as several types of tremor, bradykinesia (mild), cerebellar dysfunctions (abnormal eye blink reflex conditioning, deficits in paced finger tapping, dysfunction in hand–eye coordination and ocular movements, mirror movements, mild dysarthria, tandem gait ataxia), postural instability, olfactory and hearing deficits, and nonmotor features such as mild cognitive deficits, neuropsychiatric symptoms (anxiety, depression, specific personality traits), sleep disorders, and decreased body mass index [4].

The pathology of ET and underlying mechanisms of the disease are still unclear, but there is an increasing amount of research being conducted on the subject. There are several studies on increased Lewy body (LB) inclusions (locus coeruleus and dorsal vagus nucleus), Purkinje cell (PC) degeneration, and cerebellar pathologies. Discussions on ET's definition as a neurodegenerative disease are ongoing [5–7].

Most of the studies about nonmotor features of ET were conducted with older patients. This population may exhibit nonmotor features, such as sleep disorders, which are unrelated to the disease. To determine whether nonmotor symptoms developed as a direct outcome of the disease, or appeared as a result of the underlying mechanism, we opted to study young ET patients who had a short history of the disease. The goal of this study was to evaluate nonmotor features and to determine their effect on patient quality of life and also to demonstrate that they might occur in early stages of the disease.

Methods

74 patients with tremor (between 18 to 45 years old) who visited the outpatient unit of the Neurology Department of the Erzurum Regional Training and Research Hospital in Erzurum, Turkey between November 2012 and December 2013 were interviewed. 29 patients were excluded since they did not meet the inclusion criteria (psychiatric disease history, known sleep disorder, medication use that could adversely affect sleep quality or that could cause tremor, having another neurological disease, having tremor for less than 6 months, declining to participate, and other reasons such as being illiterate or having mental retardation). All patients had never been diagnosed or treated previously. We ruled out other possible causes of tremor using blood tests such as serum thyroid hormone, vitamin B12 levels, other biochemical blood tests (e.g., liver and kidney functions), and hemogram. Kayser–Fleischer ring for Wilson's disease was examined by an ophthalmologist. 45 patients and 35 ET-free controls were recruited for the study. All patients who had ET according to the diagnostic criteria of ET as proposed by Bain et al. were established by a neurologist [8].

The age, sex, education level, employment, and marital status-matched control group was selected from among healthy people who did not have any neurological and psychiatric disease. They did not have a history of tremor or symptoms of tremor. They were drawn from patients' relatives and voluntary university students. None of the participants had known physical causes that could affect sleep quality, such as asthma, lung disease, and thyroid dysfunction. Both groups did not use any medications that could alter psychiatric or cognitive behavior (such as anticholinergics, beta-blocking agents, antiepileptic agents, antipsychotic drugs, and antidepressive agents).

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

The patients were asked to fill out a form to record socio-demographic characteristics such as age, sex, education level, occupational and marital status, medical and family history, and duration of illness. All subjects underwent a semi-structured interview and completed the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), the Fatigue Severity Scale (FSS), the Beck Anxiety Scale (BAS), the Beck Depression Inventory (BDI), and Short Form-36 (SF-36). Cognitive functions were evaluated using the Turkish version of the Montreal Cognitive Assessment Battery (MoCA) by a neuropsychologist. Tremor rate was evaluated using the Fahn–Tolosa–Marin Tremor Rating Scale (FTM-TRS) by a neurologist.

FTM-TRS is a method for measuring resting, postural, and action tremor. There are 5 scores (0–4) for each category that represent severity. Increasing scores mean increasing severity of the disease [9].

MoCA is a rapid screening test for mild cognitive dysfunction. It assesses different cognitive domains such as attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points: a score of 21 or above is considered normal [10].

PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over the last 4 weeks. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The scoring of answers is based on a 0–3 Likert scale in which three reflects the negative extreme. A total score of ≥ 5 indicates a 'poor' sleeper [11].

ESS is a method for measuring daytime sleepiness in adults. EDS is defined as an ESS score of 10 or more. It consists of eight items. Reponses to each item are ranked from 0 to 3 according to the probability for dozing off during a task [12–15].

BDI consists of a list of descriptive statements related to 21 aspects of depression. For each category, there are four statements of increasing severity. The score for each item ranges from 0 to 3; total score falls between 0 and 63. The scores show severity of depression, 0–13: minimal depression, 14–19: mild depression, 20–28: moderate depression and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms [16–18].

BAS is a 21-question multiple-choice and self-report inventory that is used for measuring the severity of anxiety. The maximum score in the scale is 63, with 0–7: minimal level of anxiety, 8–15: mild anxiety, 16–25: moderate anxiety, and 26–63: severe anxiety. The score for each item ranges from 0 to 3 [19].

FSS is a self-reported scale. It has a nine-item questionnaire with questions related to how fatigue interferes with certain activities and rates its severity [20].

SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically based physical health (SF-36 PH) and mental health (SF-36 MH) summary measures and a preference-based health utility index [21].

Statistics

The definitive statistics in the study were summarized using arithmetic mean, mean standard deviation, etc. Numbers and percentages were used in the representation of categorical variables. The Mann–Whitney *U* tests were utilized in representation of numeric data to compare the control and patient groups under the assumption that the data were not normally distributed. Under the assumption that the data were normally distributed, independent *T* tests were utilized for the representation of numeric data to compare the control and patient groups. The comparisons for categorical variables were represented and analyzed by cross-tabulation (Chi-square). The relation between two numeric variables were represented by correlation analysis. Linear regression and multiple regression analyses were used to assess the relationship between depression and anxiety as the dependent variables and the mean MoCA total scores, the mean PSQI scores, the mean ESS scores as the independent variables. A statistical significance limit of $p < 0.05$ was used. SPSS 17.0 was used for the analysis.

Results

45 patients (mean age ± SD 24.55 ± 7.16 years; range 15–44 years) and 35 control subjects (mean age ± SD 24.80 ± 5.43 years; range 17–40 years) were enrolled in the study. There were 24 (53.3 %) women and 21 (46.7 %) men in the patient group, and 22 (62.9 %) women and 13 (37.1 %) men in the control group ($p = 0.39$). There were no statistically significant differences between the patient and control groups regarding age, gender, education level, marital status, and employment. Table 1 shows demographic characteristics for 80 study participants.

The mean duration of ET was 4.36 ± 3.94 years. Percentage of patients who had a family history of ET was 22.2 %. The mean FTM-TRS score was 10.17 ± 4.19.

Comparison of cognitive functions between patients with ET and controls

MoCA total score means were 25.80 ± 2.76 in the ET group and 28.23 ± 1.69 in the control group ($p < 0.001$). Likewise, there were statistically significant differences between the patients who did not have moderate or severe depression and the controls, when we compared the mean MoCA scores (25.96 ± 2.59, $p < 0.001$). The mean scores for 'Naming', 'Attention', 'Abstraction', and 'Orientation' were similar between each group but 'Visuospatial and executive functions', 'Language', and 'Delayed recall' subgroup scores' were higher in the control group. Table 2 shows a comparison of MoCA total scores and subgroup scores between the two groups. In addition, correlation

Table 1 Demographic characteristics for 80 study participants

	Patients ($n = 45$)	Control ($n = 35$)	*P* value*
Age (years)	24.55 ± 7.16	24.80 ± 5.43	0.87
Gender			0.39
Female	24 (53.3 %)	22 (62.9 %)	
Male	21 (46.7 %)	13 (37.1 %)	
Marital status			0.92
Single, divorced or widowed	33 (73.3 %)	26 (74.3 %)	
Married	12 (26.7 %)	9 (25.7 %)	
Education level			0.79
<11th grade	4 (8.9 %)	2 (5.7)	
High school	13 (28.9 %)	9 (25.7 %)	
University[a]	28 (62, 2 %)	24 (68.6 %)	
Employment			0.73
Student	23 (51, 1 %)	19 (54, 3 %)	
Full-time or part-time job	14 (31, 1 %)	12 (34, 3 %)	
Homemaker or unemployment	8 (17, 8)	4 (11, 4 %)	

* Chi- square test

[a] We included university students and graduate students

Table 2 MoCA total score and subgroup score means

	Patients ($n = 45$)	Controls ($n = 35$)	*P* value*
MoCA total score	25.80 ± 2.76	28.23 ± 1.69	<0.001
Subgroups			
Visuospatial/executive	3.88 ± 1.02	4.50 ± 0.44	<0.01
Naming	2.68 ± 0.51	2.86 ± 0.34	0.10
Attention	5.66 ± 0.56	5.76 ± 0.56	0.46
Language	2.33 ± 0.76	2.76 ± 0.56	0.01
Abstraction	1.66 ± 0.47	1.86 ± 0.34	0.05
Delayed recall	3.51 ± 1.21	4.23 ± 0.81	<0.01
Orientation	5.88 ± 0.31	6.00 ± 0.00	0.06

* Mann–Whitney *U* test

analysis showed that when MoCA total scores were compared across FTM-TRS score means and duration of disease, there was a negative correlation between MoCA total scores and FTM-TRS score means but this was not statistically significant ($r = -0.22$, $p = 0.88$). MoCA total score was compared with depression and anxiety using linear regression analysis. There was no association between MoCA total score and depression (OR 0.04, $p = 0.48$, 95 % CI −0.07 to 0.14) or anxiety (OR −0.04, $p = 0.47$, 95 % CI −0.13 to 0.06).

Comparison of sleep disturbance, excessive daytime sleepiness, fatigue, anxiety, and depression between each group

The score means of all tests were significantly higher in the ET group than those of the controls except for ESS. Table 3 shows a comparison of scores between ET and the controls. The percentage of subjects who had poor sleep quality defined by PSQI was 62.2 % in the patient group and 17.1 % in the control group ($p < 0.001$). Mean PSQI score was 6.31 ± 3.30 in the patient group and 3.60 ± 2.04 in the control group ($p < 0.001$). After excluding patients who had moderate and severe depression, there was still a statistically significant difference between each group ($p < 0.001$). But after excluding the patients who had moderate and severe anxiety levels, there was no difference between each group (4.23 ± 2.48, $p = 0.38$). Linear regression analysis showed that there was strong relation between disturbed sleep and anxiety (OR 0.20, $p < 0.001$, 95 % CI 0.10–0.29) but not depression.

EDS was more common in the patient group than the controls, but the difference was not found to be statistically significant (10.5 vs 8.6 %, $p = 0.50$). Mean ESS scores

Table 3 Comparison test means

Mean scores	Patients ($n = 45$)	Controls ($n = 35$)	*P* value*
PSQI total	6.31 ± 3.30	3.60 ± 2.04	<0.001
ESS	5.08 ± 4.44	5.05 ± 3.22	0.66
FSS	39.05 ± 16.94	27.34 ± 13.21	<0.01
BAS	21.73 ± 10.35	7.28 ± 6.53	<0.001
BDI	15.55 ± 9.75	7.62 ± 7.04	<0.001
SF-36 Ph	48.70 ± 8.86	52.19 ± 6.65	0.10
SF-36 Mh	38.68 ± 8.94	44.08 ± 10.48	0.02

* Mann–Whitney *U* test

were higher in the patient group than the control group but this also was not statistically significant (5.08 ± 4.44 vs 5.05 ± 3.22, $p = 0.66$). When we compared EDS and depression and anxiety, EDS was found to be associated with depression (OR 0.17, $p = 0.02$, 95 % CI 0.03–0.31, Linear regression analysis).

The percentage of subjects who had fatigue was 52.5 % in the patient group and 25.0 % in the control group ($p = 0.02$). FSS mean score was 39.05 ± 16.94 in the patient group and 27.34 ± 13.21 in the control group ($p < 0.01$). But after excluding patients who had moderate and severe depression there was no difference between each group (32.80 ± 14.71, $p = 0.15$). Fatigue was associated with depression but not anxiety (OR 0.73, $p = 0.01$, 95 % CI 0.18–1.28, Linear regression analysis).

The percentage of patients who had moderate and severe anxiety levels was 71.1 %. This ratio was 20 % in the control group. Depression was also prominent in the patient group. The percentage of patients who had moderate and severe depression levels was 35.5 %. There were two subjects (5.8 %) who had moderate and severe depression levels in the control group.

In conclusion, the prevalence of decreased quality of sleep, fatigue, anxiety and depression was significantly higher in the patient group than the controls. Table 4 shows the distribution of test subgroups.

Comparison between quality of life and sleep quality, fatigue, anxiety, and depression

When PSQI, FSS, ESS, BAS, and BDI scores were compared with SF-36 PH in the patient group, we found that fatigue, EDS, anxiety, and depression had a negative effect on physical health. Fatigue, anxiety, and depression also had a negative effect on mental health in the patient group. Table 5 shows correlations between PSQI, FSS, ESS, BAS, BDI scores and SF-36 PH, SF-36 MH scores. The patient mental health scores were lower than for the controls (38.68 ± 44.08, $p = 0.02$).

Table 4 Distribution of test subgroups

	Patients ($n = 45$)	Controls ($n = 35$)	P value*
PSQI			<0.001
≥5	28 (62.2 %)	6 (17.1 %)	
<5	17 (37.8 %)	29 (82.9 %)	
ESS			0.50
≥10	6 (10.5 %)	3 (8.6 %)	
<10	39 (89.5 %)	32 (91.4 %)	
FSS[a]			0.02
≥36	21 (52.5 %)	8 (25.0 %)	
<36	19 (47.5 %)	24 (75.0 %)	
BAS			<0.001
Minimal	4 (8.9 %)	21 (60.0 %)	
Mild	9 (20.0 %)	7 (20.0 %)	
Moderate	13 (28.9 %)	7 (20.0 %)	
Severe	19 (42.2 %)	0 (0.0 %)	
BDI			0.001
Minimal	18 (40.0 %)	29 (82.9 %)	
Mild	11 (24.4 %)	4 (11.4 %)	
Moderate	10 (22.2 %)	1 (2.9 %)	
Severe	6 (13.3 %)	1 (2.9 %)	

* Chi-square test

[a] 5 patients and 3 controls did not complete their FSS therefore 40 patients and 32 controls were evaluated

Table 5 Correlations between SF-36 and PSQI, ESS, FSS, BAS, and BDI scores (Pearson correlation analysis)

	SF-36 Ph	SF-36 Mh
PSQI		
r	−0.28	−0.14
p	0.09	0.42
ESS		
r	−0.47[a]	−0.18
p	0.003	0.28
FSS		
r	−0.43[a]	−0.50[a]
p	0.007	0.001
BAS		
r	−0.49[a]	−0.370[b]
p	0.002	0.019
BDI		
r	−0.39[b]	−0.45[a]
p	0.02	0.004

5 patients did not complete their self-writing SF-36 forms therefore 40 patients were evaluated

[a] Correlation is significant at the 0.01 level (2-tailed)

[b] Correlation is significant at the 0.05 level (2-tailed)

Discussion

In this study, we observed that mild cognitive deficit (especially visuospatial and executive functions, language, and delayed recall), depression, anxiety, sleep disturbance, and fatigue were more common in ET. However, sleep disturbance and fatigue might be related to depression anxiety. Fatigue, depression, and anxiety had a negative impact on both mental and physical health. EDS was also more common but not significant. On the other hand, EDS had a negative impact on physical health.

One of the most commonly known nonmotor features in ET is the presence of mild cognitive deficits. Gasparini et al. [22] reported a study of frontal lobe dysfunction in ET and showed that the frontal lobe feature of ET was similar to that of Parkinson's disease (PD). In the same year, Lombardi et al. [23] found deficits on tests of verbal fluency, naming, mental set-shifting, verbal memory, and working memory. Lacritz et al. [24] found that cognitive deficits were not uncommon and might be related to subcortical systems. Tröster [25] observed that the pattern of cognitive deficits was consistent with cerebello-thalamo-cortical circuit dysfunction in his study. Benito-Leon's [26] population-based case–control study showed that ET patients performed less well in test results, especially having lower global cognitive performance and frontal executive function. Sahin et al. [27] performed a study on young ET patients using a comprehensive neuropsychological test battery and they found subclinical cognitive deficits characterized by visuospatial and verbal memory impairments and executive dysfunction. We used the MoCA test in our study and had similar findings. This is important for two reasons: this study showed that young ET patients might exhibit cognitive impairment as a part of the disease and this can be detected using an easily applicable test. Kim and Louis [28, 29] studies showed lower cognitive test scores that were correlated with tremor severity and functional difficulty. We also found a negative correlation between MoCA scores and tremor severity but it was not statistically significant. Besides all of these cognitive deficits, ET was found to be associated with increased risk of dementia [30, 31]. These studies showed us that the cerebello-thalamo-frontal pathway has a role in the pathology of ET. In our study, we observed that even a young population with ET could have mild cognitive deficits. 'Visuospatial and executive functions', 'Language' and 'Delayed recall' functions were particularly affected, and this could be determined using a rapid screen test such as MoCA.

There are significant relations between depression and ET, and a significant risk of developing ET [32]. Contrary to the ordinary hypothesis, this shows that depression can be a part of underlying mechanisms of the disease and not a result of the disease. Depressive symptoms were a stronger predictor of tremor-related quality of life than tremor itself [33]. Therewithal, Chandran et al. [34] determined that depression and anxiety were related to the quality of life. We found that depression and anxiety were more common in young patients with ET, and they affected the mental and physical quality of life regardless of the level of tremor.

Lewy bodies have been described in the locus coeruleus in ET patients; this brainstem nucleus plays a role in sleep. Poor nocturnal sleep quality and sleep disturbances have also been found to be related to ET. Chandran et al. [35] found that poor sleep quality without excessive daytime sleepiness was probably due to depression. Adler et al. [36] studied REM sleep behavior disorder (RBD). The prevalence of RBD was similar to controls. Gerbin et al. [37] found that some sleep scores in ET were intermediate between PD and normal controls, suggesting that a mild form of sleep dysregulation could be present in ET. Benito-Leon [38] determined that short daily sleep duration might be a pre-motor marker of ET. Sleep disturbances are common in the older population but we studied patients with ages between 18 and 45. The percentage of subjects who had poor sleep quality was 63.2 % in the patient group and 13.3 % in the control group. Although there was an apparent difference between the two groups, we found that poor sleep might be associated with increased anxiety levels.

Fatigue was found more often in the ET group. On the other hand, when we compared the patients who did not have moderate and severe depression, there was no difference from the controls. This was one of the reasons for a negative effect on SF-36 PH and SF-36 MH. Other reasons for the negative affect on both physical and mental health were depression and anxiety.

This study had some limitations, such as that cognitive testing was limited to MoCA. Nevertheless, this test is easy to apply in clinical practice. We used the Turkish version of MoCA, which was a new instrument. The other tests we used were filled out by the subjects and there was no psychiatric interview with the subjects beforehand. The number of subjects that we studied was small. We mostly ruled out possible causes of tremor but not Fragile X syndrome. We did not ask subjects about smoking habits and caffeine/stimulant consumption. Studying young patients while at the same time looking into multiple nonmotor features was the strong part of this study.

There is increasing interest in nonmotor features of ET. The aim of this study was to contribute to this new concept. The emergence of nonmotor symptoms, particularly at a young age, may indicate that these symptoms could be a part of the disease. Further studies of nonmotor features will go a long way in understanding ET. The identification of nonmotor findings and their underlying physiological and anatomical causes is of crucial importance in shedding light on previously unknown aspects of the disease.

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

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