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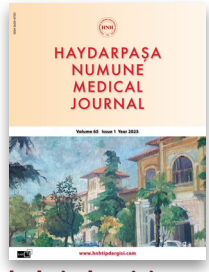

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ORIGINAL ARTICLE

Essential Tremor Non-Motor Symptoms: A Single Center Study

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Abstract

Introduction: Essential tremor (ET) is the most common movement disorder, and studies suggest that in addition to motor symptoms, there may also be non-motor symptoms. In this study, we aimed to investigate the clinical characteristics and the impact of disease severity on daily life in Turkish patients with ET.

Methods: Thirty patients with ET and 30 gender-matched healthy controls were included. The Montreal Cognitive Assessment (MoCA), Pittsburgh Sleep Quality Index (PSQI), Non-Motor Symptoms Questionnaire (NMSQ), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) were utilized to assess and compare psychiatric and cognitive status and sleep disturbances, and to investigate whether these symptoms are related to the severity of motor symptoms. Tremor severity was evaluated by the Fahn–Tolosa–Marin Tremor Rating Scale (FTM-TRS).

Results: The average BDI, BAI, and NMSQ scores were significantly higher in the patient group ($p<0.005$). A positive correlation was observed between disease duration and PSQI, BAI, and NMSQ scores ($p=0.028$, $p=0.041$, $p=0.047$, respectively). FTM-TRS scores showed a negative correlation with MoCA and a positive correlation with PSQI, BDI, BAI, and NMSQ scores ($p=0.005$, $p<0.001$, $p=0.005$, $p=0.004$). The average MoCA score in patients over 45 years old was significantly lower ($p=0.008$).

Discussion and Conclusion: Our results indicated that non-motor symptoms such as anxiety, decreased sleep quality, and impaired cognitive functions accompanying ET significantly affect patients' quality of life. Therefore, evaluating and treating non-motor symptoms should be considered essential for the rehabilitation of patients with ET.

Keywords: Anxiety; cognition; depression; essential tremor; non-motor symptoms; sleep quality.

In adults, essential tremor (ET) is a common movement disease mostly affecting the hands and arms, characterized by simple kinetic and/or postural tremor, which may be accompanied by voice, neck, and head tremors.[1] Research on ET is increasing, despite the fact that its pathophysiology and underlying processes are still unknown. Numerous investigations have been conducted on Purkinje cell degeneration, cerebellar disorders, and increased Lewy body inclusions (locus coeruleus and dorsal vagus nucleus). There are ongoing discussions on the definition of ET as a possible neurodegenerative disease.[2,3] According to reports, 3% of Turkish adults over the age of 18 have ET, and the prevalence of potential essential tremor cases in Turkish adolescents was 0.41%, which supports the idea that ET is a prevalent movement disorder in the Turkish population.[4]

In addition to motor symptoms, numerous non-motor symptoms (NMS) such as pain, cognitive abnormalities, anxiety and depression, hearing impairment, and poor sleep have been reported in patients with ET in various studies conducted in different populations.[5–8] More than 20 years ago, Louis et al.[9] and Lombardi et al.[10]

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were the first researchers to characterize ET as more than just a motor disorder. The ET spectrum now includes a variety of non-motor characteristics, making it essential to understand the condition's pathogenesis and link its features to the clinical symptoms seen in patients. In addition to the tremor-induced disability of essential tremor patients, the recognition of NMS such as cognitive impairment, decreased sleep quality, bowel problems, decreased sense of smell, depression, and anxiety—which negatively affect their quality of life—may contribute to the rehabilitation of patients. However, there is limited data regarding the NMS features of Turkish patients with ET in the current literature.

The aim of this study was to evaluate NMS including sleep quality, depression, anxiety, and cognitive functions in Turkish patients with ET and to compare the symptom frequency of patients with healthy individuals. In addition, the effect of age was analysed by comparing early (≤45 years) and advanced (>45 years) age groups of patients.

Materials and Methods

This single-center, cross-sectional, observational, case–control study was carried out in compliance with the Helsinki Declaration. The study was approved by the ethics committee of our hospital (Number: HNEAH-KAEK 2023/KK/18). After providing their written consent, participants were informed about the voluntary consent form and included in the study.

Participants

In this study, 30 consecutive patients over the age of 18 who presented to our outpatient clinic for movement disorders between February 2023 and July 2023 with action tremor in both upper extremities and were diagnosed with ET according to IPMDS 2018 Tremor Task Group criteria,[11] and 30 sex- and age-matched healthy controls were recruited. Patients with drug exposure, toxicity, and systemic diseases known to cause tremor; patients with neurological diseases such as demyelinating diseases, cerebrovascular diseases, peripheral neuropathy, parkinsonism, dystonia, and spinocerebellar ataxia; patients under 18 years of age; and patients with limited cooperation were excluded from the study.

Instruments

Patients who agreed to participate in the study underwent neurological examination. Laboratory and neuroimaging examinations (Computed Tomography (CT), Magnetic Resonance Imaging (MRI)) were recorded. Sociodemographic characteristics of the patient and control groups and their backgrounds were collected. Pittsburgh Sleep Quality Index (PSQI) was used for sleep quality, Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) for anxiety and depression, Montreal Cognitive Assessment (MoCA) for cognitive impairment, and Non-Motor Symptoms Questionnaire (NMSQ) for other non-motor symptoms. In the patient group, disease history and medications were recorded, and the Fahn–Tolosa–Marin Tremor Rating Scale (FTM-TRS) was applied to determine the severity of the disease.

Sociodemographic Clinical Form

It was a form created by the researchers and used to evaluate the sociodemographic characteristics of the participants and information about their complaints related to ET. Gender, age, education level, marital status, smoking, alcohol consumption, family history of movement disorders, medical history, duration of ET, and medications for it were questioned.

Fahn–Tolosa–Marin Tremor Rating Scale (FTM-TRS)

It is a scale in which resting, action, and postural tremor can be evaluated.[12] Severity is scored on a 5-point scale. An increase in the score indicates an increase in the severity of the disease. It has international validity in the clinical evaluation and follow-up of essential tremor and is currently used. The scale's validity and reliability in Türkiye were investigated by Yaka et al.[13]

Beck Anxiety Inventory (BAI)

This Likert-type scale, consisting of 21 questions by Aaron Beck, is used to indicate the anxiety level of individuals aged 12 years and older.[14] The scores of the ticked options are summed, and the evaluation is made according to this score. The validity and reliability of this scale have been performed in Türkiye.[15]

Beck Depression Inventory (BDI)

It evaluates the physical, emotional, cognitive, and motivational symptoms associated with depression.[16] There are four options in each of 21 categories of symptoms. A high total score indicates a high severity of depression. National validation was performed.[17]

Pittsburgh Sleep Quality Index (PSQI)

It is a questionnaire designed to assess sleep quality through seven main categories, including subjective sleep quality, sleep onset latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medication usage, and daytime functioning. A total score of ≥5 is considered poor sleep quality. The national validity and reliability of this scale were performed by Ağargün et al.[18]

Montreal Cognitive Assessment (MoCA)

This test evaluates concentration, attention, memory, executive functions, language, visual reconstruction, abstract thought, calculation, and orientation skills. Its Turkish validity and reliability were performed by Selekler et al.[19]

NMSQ (Non-Motor Symptoms Questionnaire)

The NMSQ is a 30-item patient-based screening tool that can be self-completed and answered as "yes" or "no" to each item. Scores are graded according to the points obtained.[20]

Statistical Analysis

Data collection and analysis were conducted using the Statistical Package for the Social Sciences (SPSS) software, version 25.0. The Kolmogorov–Smirnov test and histogram diagrams were used to examine whether the variables conformed to a normal distribution. Descriptive analyses were conducted using the mean, standard deviation, median, and minimum–maximum values. The findings of 2×2 tables were compared using the Pearson Chi-Square test. Nonparametric (nonnormally distributed) variables were compared between groups using the Mann–Whitney U test. The measured data were compared using Spearman's correlation test. Results with $p<0.05$ were considered statistically significant.

Results

Our research involved a total of 60 participants, with half assigned to the essential tremor (ET) group and the remaining half forming the healthy control group, each consisting of 30 individuals. There was no significant difference between the groups regarding age and gender. Table 1 demonstrates the demographic characteristics of the participants. There were 20 (33.3%) primary school graduates, 21 (35%) high school graduates, and 19 (31.6%) university graduates.

The comparison of patient and control groups' test scores is demonstrated in Table 2. In the patient group, the MoCA scores were significantly lower than those of healthy subjects ($p<0.05$). PSQI scores did not show a significant difference ($p>0.05$). The mean scores of BDI, BAI, and NMSQ in the patient group were found to be significantly higher than those of the control group ($p=0.014$, $p<0.001$, $p=0.023$, respectively).

The results of the MoCA test did not show a significant distinction between the two groups regarding the mean scores of 'naming', 'attention', 'abstraction', and 'language' ($p>0.05$), whereas the scores of 'visuospatial and executive functions', 'delayed recall', and 'orientation' subgroups were significantly higher in the control group ($p=0.024$, $p=0.007$, $p=0.003$, respectively).

The correlation between the duration of tremor (years) and MoCA, PSQI, BDI, BAI, and NMSQ test results was analyzed. A positive correlation was found between the onset of the disease and PSQI, BAI, and NMSQ scores ($p=0.028$, $p=0.041$, $p=0.047$, respectively).

The correlation between FTM-TRS results and baseline duration (years), MoCA, PSQI, BDI, BAI, and NMSQ results

Table 2. The comparison of the scores of scales between the groups

	ET Median (Min-Max)	Control Median (Min-Max)	p
MoCA	23.5 (8-28)	25.5 (17-30)	0.033
PSQI	7 (0-18)	4.5 (1-10)	0.107
BDI	8 (1-31)	4 (0-23)	0.014
BAI	12.5 (3-33)	4 (0-20)	<0.001
NMSQ	6 (0-18)	4 (0-15)	0.023

Mann Whitney-U Test; ET: Essential Tremor; MoCA: Montreal Cognitive Assessment; PSQI: Pittsburgh Sleep Quality Index; NMSQ: Non-Motor Symptoms Scale; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory.

Table 1. The comparison of age and gender between the groups

	Participants				p
	Patient Group (ET)		Control Group		
	n	%	n	%	
Gender					
Female	13	(43.33)	18	(60.00)	0.196
Male	17	(56.67)	12	(40.00)	
Age*	47.53±18.46	52 (18-82)	51.17±15.31	53 (19-74)	0.429

ET: Essential tremor; Chi-Square Test * Mann Whitney-U Test n= Number of patients.

was analyzed. There was a negative correlation between FTM-TRS and MoCA scores; whereas, there was a positive correlation with PSQI, BDI, BAI, and NMSQ test scores (p=0.005, p<0.001, p=0.005, p=0.004).

We did not find a significant difference between the results of the scales in ET patients with additional tremor and those without additional tremor.

Patients and controls were divided into two subgroups as younger age group (≤45 years) and older age group (>45 years) for detailed analysis to explore the effect of age. The mean age of the younger age ET group was 30.1±7.67, and the mean age of the control group was 31.5±6.9 (p=0.688). The mean age of the older age ET group was 62.7±8.8, and the mean age of the control group was 59.5±8.5 (p=0.387). There was no significant difference according to age group.

The mean results of tremor duration (years), MoCA, PSQI, BDI, BAI, NMSQ, and FTM-TRS were compared between age groups in the ET group. In patients aged ≤45 years, the mean MoCA was found to be higher (p=0.001), and the mean FTM-TRS result was found to be lower (p=0.004) than in ET patients aged >45 years (Table 3).

The mean scores of MoCA, PSQI, BDI, BAI, and NMSQ were compared between the ET and control groups in subgroups aged ≤45 years and >45 years. Specifically, the mean BAI score in patients with ET aged ≤45 years was found to be significantly higher than that in controls of the same age group (p=0.039). However, the rate of moderate and severe anxiety in the ET group was 28.5%, while in the control group, it was 11.1%, and no significant difference was observed (p=0.281).

The comparison of subgroups aged >45 years in control and patient groups is illustrated in Table 4. In the patient group, the average MoCA score of individuals over 45 years old was lower compared to the control group, while the mean PSQI, BDI, BAI, and NMSQ scores were higher (p<0.05). No significant difference was observed in the prevalence

Table 3. The comparison of the scale scores between age groups in the patient group

	ET				p
	≤45 years (n=14)		>45 years (n=16)		
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
Duration of Tremor (years)	10.36±4.81	10 (3-20)	12.81±13.47	8.5 (3-50)	0.498
MOCA	25.71±2.95	27 (19-28)	18.88±5.75	20 (8-28)	0.001
PSQI	5.14±3.53	5 (1-12)	8.75±5.6	10.5 (0-18)	0.064
BDI	8.64±7.81	7 (1-26)	13±8.95	9 (3-31)	0.120
BAI	13.57±9.6	11 (3-33)	15.38±8.81	15 (5-31)	0.498
NMSQ	5.79±4.35	5.5 (0-14)	8.12±4.87	8.5 (1-18)	0.193
FTM-TRS	13.21±8.23	11 (5-38)	23.75±10.69	23 (7-41)	0.004

Mann Whitney-U Test; ET: Essential Tremor; MoCA: Montreal Cognitive Assessment; PSQI: Pittsburgh Sleep Quality Index; NMSQ: Non-Motor Symptoms Scale; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; FTM-TRS: Fahn-Tolosa-Marin Tremor Rating Scale.

Table 4. The comparison of subgroups aged > 45 years in control and ET groups

	ET >45 years		Control >45 years		p
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
MOCA	18.88±5.75	20 (8-28)	23.67±3.76	24 (17-29)	0.008
PSQI	8.75±5.6	10.5 (0-18)	4.57±2.77	4 (1-10)	0.019
BDI	13±8.95	9 (3-31)	4.9±5	3 (0-23)	<0.001
BAI	15.38±8.81	15 (5-31)	4.24±3.66	3 (0-16)	<0.001
NMSQ	8.12±4.87	8.5 (1-18)	4.33±2.5	4 (1-10)	0.012

Mann Whitney-U Test; ET: Essential Tremor; MoCA: Montreal Cognitive Assessment; PSQI: Pittsburgh Sleep Quality Index; NMSQ: Non-Motor Symptoms Scale; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory.

of moderate and major depression between the patient and control groups over 45 years old (p=0.105). However, the rate of moderate and severe anxiety was significantly higher in the patient group (p=0.008).

Discussion

This study aimed to assess various non-motor symptoms related to ET and their relationship with disease duration, severity, and age, in addition to investigating their association with characteristics of healthy individuals. Our findings revealed that non-motor symptoms such as anxiety, reduced sleep quality, and cognitive impairment associated with ET had a significant impact on patients' quality of life, confirming the importance of non-motor symptoms as a component of ET, in accordance with the current literature.

One of the most commonly recognized non-motor features in ET is the presence of mild cognitive impairment. Many studies have shown that ET patients have more cognitive impairment than age-matched controls.[21] It has been reported that cognitive changes may occur even before the motor symptoms of ET.[22] ET patients and matched healthy controls from Egypt were analyzed in a recent case–control observational study, and the results demonstrated that ET patients showed severe cognitive impairment.[23] In a study by Sengul et al.,[24] the authors investigated cognitive functions, depression, anxiety, fatigue, and sleep disturbances in young patients with ET. Similar to our findings, that study demonstrated that poor sleep quality, fatigue, anxiety, depressive symptoms, and lower MoCA total scores were observed in patients with ET. The results of this study showed that MoCA test scores were significantly lower in the ET group compared to healthy controls. We also found a statistically significant negative correlation between MoCA scores and tremor severity, which was consistent with previous studies.[25] When analyzed according to age groups, we found that MoCA values were significantly lower in patients over 45 years of age compared to controls. In the MoCA subgroup analysis, we found that "visuospatial and executive functions", "delayed recall", and "orientation" functions were affected, similar to previous studies.[24]

Prospective studies have described mild deficits in attention, executive function, memory, and language following a progressive course in patients with ET.[26,27] These studies suggest that the cerebello-thalamo-frontal pathway plays a role in ET pathology. The fact that low MoCA values are associated with disease severity and are significantly lower in all patients compared to controls supports the idea that cognitive impairment has a clinical correlation and may play a role in the pathogenesis of ET as part of the disease process.[3]

Numerous studies indicate that individuals with ET experience a greater number of depressive symptoms and may even have a higher occurrence of depression compared to the general population. Similar to a Turkish study, patients with ET had higher depression scale ratings than controls, and there was a positive correlation between these scores and tremor severity.[28] Our findings are in accordance with other clinical studies investigating the effects of depression and disease severity. In contrast, in previous studies using the Geriatric Depression Scale (GDS), significant depression was reported in ET, but no correlation was found with tremor severity,[10] and in a recent study, a non-significant difference was found in GDS.[29] This may be explained by cultural and psychosocial differences among patients with ET. In our study, BDI scores were significantly higher in the ET group compared to the control group. Although the rate of moderate and major depression was higher than in the control group, the difference was not statistically significant. However, there was a significant correlation between tremor severity and BDI scores, suggesting that, consistent with previous research, depressive symptoms may be related to tremor severity.[28]

A recent study in China reported a significant prevalence of depression (more than half of the cases), particularly in women, those with head or voice tremors, and those with significant functional impairment.[30] Our results are in contrast to this study. In our study, no significant difference was found between the scales in the group with additional tremor accompanying hand tremor. These variable findings may be explained by the use of different scales and the variable number of ET patients included in each study.

In Türkiye, 35 controls and 45 ET cases were studied. The study found that the BAI scores of the cases were significantly higher, and 71.1% of the patients had moderate to severe anxiety levels (BAI≥16), compared to only 20.0% of the controls.[24] In our study, similar to depression, anxiety scores were higher in the ET group compared to controls and correlated with disease duration and severity. ET patients over 45 years of age had statistically significantly higher BAI scores and rates of severe and moderate anxiety among non-motor symptoms compared to the control group. The relationship between anxiety and ET severity is a matter of debate. Some studies have found a correlation,[31] while others have shown no correlation.[32]

It is believed that the connections within the cerebellothalamocortical pathway, paralimbic and limbic systems, and prefrontal cortical area-which are considered significant in the pathophysiology of ET-play a role in ET-related depression and anxiety.[33] Although improvements in the scales after treatment support the idea that anxiety is a comorbid psychiatric condition during the disease in ET patients, the anatomical structures involved in the pathophysiology of ET suggest that there may be an organic connection between ET and anxiety. In our study, the correlation with the duration, severity, and age of the disease suggests compatibility with a comorbid psychiatric condition.

Sleep disturbances are attracting increasing attention in Parkinson's disease and other movement disorders. Recent studies have demonstrated the presence of sleep problems in patients with ET.[24,31] In our study, it was detected that PSQI score was correlated with the severity and duration of the disease. We implicated that patients with ET had poor sleep quality in accordance with previous studies, but it was not statistically significant. Sleep quality scores were higher in ET patients with moderate and severe anxiety and depression scores. This reveals that as the psychiatric symptoms of the patients increase, sleep disturbance also shows a correlated increase.

Unfortunately, there is no special scale developed for non-motor symptoms in essential tremor patients, and the NMSQ scale—originally used for Parkinson's patients in 2006, which includes parameters such as autonomic, sleep, and depressive symptoms—was used in this study.[20] In our study, the NMSQ scores of the patients were statistically significant compared to the control group, as expected. In addition, we found a positive correlation between the severity of the disease and the NMSQ scale scores of our patient sample. These findings are compatible with the literature.[34] In patients above 45 years of age, the NMSQ score was found to be significantly higher compared to controls, whereas the mean value was found to be higher in patients aged ≤45 years, although not significantly. The severity of the disease, regardless of age, reinforces the hypothesis that non-motor symptoms are a characteristic feature specific to ET.[29,34]

We acknowledge that this study has several limitations. The use of self-reported inventories and the limited sample size are two examples of these. However, one of the study's strengths is that we contrasted our findings with those of healthy individuals. Moreover, we evaluated psychiatric symptoms, sleep quality, and motor functions using objective and validated inventories. Furthermore, all scales were examined both in ET patients with accompanying additional tremor and in those without additional tremor.

Conclusion

All of these results point to the need for an assessment of ET—the most prevalent movement disorder in adults—not only from the perspective of physical limitations but also from a psychosocial point of view. Additional research that supports this multifaceted assessment will help to clarify the disorder's etiopathology and improve treatment outcomes.

***The paper has been presented in 59th National Neurology Congress (e poster with discussion).*

Ethics Committee Approval: The study was approved by Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (No: 2023/KK/18, Date: 06.02.2023).

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