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Tremor and Other Hyperkinetic Movements

Brief Reports

Clinical Profile of Non-Motor Symptoms in Patients with Essential Tremor: Impact on Quality of Life and Age-Related Differences

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Abstract

Background: Identifying the clinical phenotypes of non-motor symptoms (NMSs) of essential tremor (ET) among different populations is necessary due to their impact on the quality of life (QoL). This study aimed to investigate the clinical phenotype and impact of NMSs on QoL in Egyptian patients with ET.

Methods: Thirty ET patients were compared to 30 matched controls. Subjects were evaluated by the Fahn-Tolosa-Marin Tremor Rating Scale, Non-Motor Symptoms Scale (NMSS), Montreal Cognitive Assessment, Hamilton Anxiety Rating Scale, Beck Depression Inventory, Pittsburgh Sleep quality Index, and the Short Form 36 Health Survey Questionnaire. Both groups were divided into two subgroups of younger (<45 years, 14 patients) and older age (>45 years, 16 patients) groups, to investigate age-related differences.

Results: ET patients showed significantly worse cognition, depression, anxiety, sleep and NMSS domains ($p < 0.001$), compared to controls, that negatively affected and predicted QoL. Older patients had more cognitive impairment ($p = 0.003$) and worse sleep/fatigue ($p = 0.032$) and sexual functions ($p = 0.006$), compared to younger group.

Discussion: The study supports that NMSs are integral part of ET, negatively affect QoL, and similarly affect younger and older patients. Therefore, NMSs should be explored for proper care of ET patients.

Keywords: Essential tremor, non-motor symptoms, quality of life, cognitive deficit, sleep quality

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Supplementary material: To access the supplementary material, please visit the article landing page.

Introduction

Essential tremor (ET) is one of the most common tremor disorders, which is characterized mainly by the presence of action tremor of the hands. Abnormalities in the cerebellothalamocortical loop have been implicated in the neuropathogenesis of ET.[1] Apart from motor features, significant non-motor symptoms (NMSs) were reported in patients with ET by several studies in different populations, including cognitive abnormalities, anxiety and depression, pain, hearing impairment, and poor sleep.[2–7] However, further studies are warranted to explore the biological bases of these non-motor features and the clinical differences among different populations.[8]

Recent studies confirmed the impact of NMSs on patients' quality of life (QoL), which emphasized the importance of evaluation of these symptoms in the management of patients with ET. However, the controversy about the nature of these NMSs as an intrinsic part of ET, or secondary to tremor severity, has been provoked.[9] In addition to NMSs, other factors, such as age, neuroticism, and tremor severity, were correlated to impaired QoL of ET patients.[2,8]

Therefore, the current study aimed to investigate the non-motor features, including depression, anxiety, sleep quality, and cognitive functions, in Egyptian patients with ET compared to healthy controls and their impact on patients' QoL. Furthermore, the impact of age was studied by comparing early (≤45 years) and older (>45 years) age groups.

Methods

Thirty patients with ET and 30 sex- and age-matched healthy controls were included in this prospective study. Patients were recruited from outpatient movement disorders clinic at Ain Shams University Hospitals from December 2017 to September 2018. Patients with ET were diagnosed according to International Parkinsonism and Movement Disorder Society (MDS) diagnostic criteria.[10] Exclusion criteria included patients with diagnosis of tremor of other etiologies (PD, dystonia, enhanced physiological tremor, etc.), concurrent or recent exposure to tremorogenic drugs, trauma within 3 months before the onset of tremor, and inability of the patient to perform the tests. The matched controls were recruited from healthy persons who accompanied patients to the outpatient clinic and were assessed to exclude ET or the presence of family history of tremor. All subjects were non-alcoholics according to culture norms and did not take any antidepressants. The study was approved by the Ethical Committee of the Faculty of Medicine, Ain Shams University, which is consistent with the ethical standards of the Declaration of Helsinki. An informed consent was provided from all recruited subjects.

Patients with ET were subjected to comprehensive history, including medical comorbidities, and examination, and they were evaluated by Fahn Tolosa Marin Tremor Rating Scale (FTMRS) for tremor severity; Non-Motor Symptoms Scale (NMSS) for NMSs[11]; the Montreal Cognitive Assessment (MoCA) – Arabic version for cognitive functions[12]; Beck Depression Inventory (BDI) for depression[13]; Hamilton Anxiety Rating Scale (HARS) for anxiety[14]; Pittsburgh Sleep Quality Index (PSQI) for sleep problems[15]; and the Arabic version of Short Form 36 Health Status Questionnaire (SF-36) for QoL.[16]

Power analysis calculation for sample size based on previous studies was performed using ClinCal software. Calculation yielded a power of 80% in case of using 31 per group.

Statistical analysis

The collected data were analyzed using the Statistical Package for Social Science (SPSS version 20). Non-numerical data were described as frequency and percentage; parametric numerical data were presented as mean, standard deviation (± SD) and range; while non-parametric data were presented as median and interquartile range (IQR).

The parametric data of the two study groups were compared by the independent student *t*-test. Correlations of NMSs were performed by the Pearson correlation coefficient. Regression analysis was used to detect predictors of QoL of the patients group.

Results

The mean age of ET patients was 45.20 ± 18.10 (range 18–76 years) and the mean age of control subjects was 43.43 ± 17.27 (range 19–77). The cases and control subjects were age- and sex-matched. The mean age of onset of ET was 34.73 ± 16.56 years (range 10–63), the mean illness duration was 10.40 ± 7.86 years (3–30), and the mean FTM-TRS score was 42.10 ± 13.80 (Table 1). Seventeen patients (42.5%) reported positive family history of ET, and six patients had comorbidities, including hypertension, diabetes, and benign prostate hypertrophy (3, 2, and 1 patient, respectively). No patients reported taking medications that might affect NMSs, with only four patients receiving propranolol to ameliorate tremor.

Comparison of NMSs and QoL between ET patients and the control group

There were significant differences in all tests between ET patients and controls (Table 1). Patients with ET showed more cognitive impairment (lower MoCA) ($p = 0.021$), the significant difference in MoCA subtests was mainly in visuospatial/executive functions, recall and naming ($p < 0.001$; 0.006; 0.035, respectively). Also, patients showed more depressed mood (higher BDI) ($p = 0.001$), more anxiety (higher HARS) ($p \leq 0.001$), and worse sleep quality (higher PSQI) ($p = 0.016$), compared to controls. Patients' total NMSS and most of its domains showed highly significant worse NMSs compared to controls ($p < 0.001$). Impaired sleep/fatigue, mood/cognition, and memory/attention domains were reported by all ET patients (100%), while impaired urinary (30%) and gastrointestinal (43.3%) domains were less reported. ET patients showed statistically highly significant impairment (lower scores) on all QoL subscales, compared to controls ($p \leq 0.001$) (Table 1).

Correlations of neuropsychiatric and NMSS with age, illness duration, and tremor severity

Total NMSS score was positively correlated to age of onset ($r = 0.422$, $p = 0.020$) and tremor severity ($r = 0.389$, $p = 0.033$). Fatigue/sleep domain was positively correlated with age ($r = 0.525$, $p = 0.003$) and age of disease onset ($r = 0.486$, $p = 0.006$), while cardiovascular and attention/memory domains were correlated to tremor severity ($r = 0.567$, $p = 0.001$ and $r = 0.519$, $p = 0.003$, respectively) (Supplementary Table A).

MoCA total score was negatively correlated with age ($r = -0.612$, $p < 0.001$) and age of onset ($r = -0.691$, $p < 0.001$), but there was no correlation with duration or with tremor severity. Depression was positively correlated with tremor severity ($r = 0.389$, $p = 0.033$), while anxiety and PSQI showed no correlation with age, age of onset, illness duration or with severity of tremor (Supplementary Table A).

Correlations of HRQoL in ET patients

All QoL subscales were negatively and significantly correlated with tremor severity (FTMRS) except social functioning ($r = -0.348$, $p = 0.059$), which means increased severity of tremor leads to more impairment and poor general health status. All QoL subscales were negatively correlated with depression, while anxiety was negatively correlated with physical functioning ($p = 0.042$), mental health ($p = 0.002$),

Table 1. **Comparison of NMSs and QoL between ET Patients and Controls**

	ET patients	Controls	p*
	N = 30	N = 30	
Age	45.20 ± 18.10 (18–76)	43.43 ± 17.27 (19–77)	0.700
FTMRS_TOTAL	42.10 ± 13.80 (19–79)		
(1) Tremor severity	17.10 ± 6.20 (7–33)		
(2) Handwriting	15.73 ±5 .30 (8–28)		
(3) Functional disability	9.40 ± 3.59 (4–18)		
MoCA	25.73 ± 3.04 (21–30)	27.40 ± 2.34 (24–30)	0.021
BDI	13.33±6.00 (70%)	8.77 ± 4.16 (26.7%)	0.001
HARS	15.67 ± 6.25	9.70 ± 4.47	<0.001
PSQI	6.13 ± 2.87	4.40 ± 2.53	0.016
Non-motor symptoms scale*			
NMSS Total	58.03 ± 21.50 (100%)	17.20 ± 11.80 (96.7%)	<0.001
(1) Cardiovascular	4.17 ± 3.60 (80%)	1.00 ± 1.51 (43.3%)	<0.001
(2) Sleep/fatigue	10.53 ± 6.07 (100%)	4.10 ± 3.52 (80%)	<0.001
(3) Mood/cognition	17.57 ± 7.67 (100%)	5.43 ± 3.77 (83.3%)	<0.001
(4) Perceptual problems	1.37 ± 1.87 (46.6%)	0.23 ± 0.63 (13.3%)	0.003
(5) Attention/memory	8.13 ± 5.19 (100%)	2.83 ± 3.09 (73.3%)	<0.001
(6) Gastrointestinal symptoms	1.50 ± 2.70 (43.3%)	0.17 ± 0.46 (13.3%)	0.010
(7) Urinary symptoms	1.10 ± 1.90 (30%)	0.33 ± 0.71 (20%)	0.043
(8) Sexual function	4.13 ± 3.51 (70%)	0.53 ± 1.25 (16.7 %)	<0.001
(9) Miscellaneous	9.53 ± 4.88 (96.6%)	2.57 ± 3.01(56.7%)	<0.001
HRQoL Subscales**			
(1) Physical Functioning (PF)	57.17 ±11.24	79.15±11.43	<0.001
(2) Role physical (RP)	58.12±10.23	77.43±9.72	<0.001
(3) Bodily pain (BP)	58.42±11.43	76.25±7.200	<0.001
(4) General health (GH)	61.72±10.881	77.92±11.077	<0.001
(5) Vitality (VT)	54.23±11.80	74.93±9.44	<0.001
(6) Role-emotional (RE)	52.25±11.62	77.63±8.32	<0.001
(7) Mental health (MH)	51.47±11.13	76.58±11.864	<0.001
(8) Social functioning (SF)	52.71±9.31	75.40±9.062	<0.001

Abbreviations: BDI, Beck Depression Inventory; HARS, Hamilton Anxiety Rating Scale; MoCA, Montreal Cognitive Assessment; NMSS, Non-Motor Symptoms Scale; PSQI, Pittsburgh Sleep Quality Index; SD, Standard Deviation. $p < 0.05$: significant; $p < 0.001$: highly significant; * Compared by student's *t*-tests.*Higher scores indicate worse functions.** The physical components of SF-36 include PF, RP, BP, and GH scales, whereas mental components include VT, SF, RE, and MH scales. Higher scores reflect better health status.

role-physical ($p = 0.025$) and role-emotional ($p = 0.010$). Role-emotional limitations were negatively correlated with sleep quality ($r = -0.417$, $p = 0.022$) and mental health was positively correlated with MoCA scores ($r = 0.515$, $p = 0.004$) (Supplementary Table B).

QoL subscales were negatively correlated with total and most of the domains of NMSS, except perceptual problems, gastrointestinal tract and urinary symptoms, which means that an increased severity of NMSs is associated with more impairment of QoL, as shown in Table 2.

Predictors of HRQoL in ET patients

Linear regression analysis showed that the total NMSS was the main predictor of all QoL domains of ET patients ($p < 0.001$). MoCA score

Table 2. **Correlations of HRQoL with NMSs in ET Patients**

		PF	RP	RE	VT	MH	SF	BP	GH
Cardiovascular	r	−0.674	−0.623	−0.642	−0.697	−0.610	−0.536	−0.560	−0.627
	p	*<0.001**	*<0.001**	*<0.001**	*<0.001**	*<0.001**	*0.002**	*0.001**	*<0.001**
Sleep/fatigue	r	−0.601	−0.597	−0.680	−0.553	−0.701	−0.619	−0.515	−0.513
	p	*<0.001**	*<0.001**	*<0.001**	*0.002**	*<0.001**	*<0.001**	*0.004**	*0.004**
Mood/cognition	r	−0.640	−0.693	−0.692	−0.547	−0.631	−0.588	−0.561	−0.587
	p	*<0.001**	*<0.001**	*<0.001**	*0.002**	*<0.001**	*0.001**	*0.001**	*0.001**
Perceptual abnormalities	r	−0.064	0.076	0.017	−0.021	0.157	0.205	0.027	−0.113
	p	0.738	0.689	0.929	0.911	0.408	0.276	0.889	0.553
Attention/memory	r	−0.467	−0.408	−0.683	−0.688	−0.677	−0.622	−0.474	−0.585
	p	*0.009**	*0.025**	*<0.001**	*<0.001**	*<0.001**	*<0.001**	*0.008**	*0.001**
Gastrointestinal	r	−0.182	−0.177	−0.354	−0.293	−0.178	−0.311	−0.259	−0.344
	p	0.335	0.349	0.055	0.117	0.346	0.094	0.167	0.063
Urinary	r	−0.185	−0.176	−0.082	−0.163	0.009	−0.015	−0.162	−0.074
	p	0.328	0.351	0.668	0.391	0.962	0.935	0.394	0.699
Sexual function	r	−0.420	−0.334	−0.335	−0.539	−0.249	−0.392	−0.393	−0.275
	p	*0.021**	0.071	0.070	*0.002**	0.185	*0.032**	*0.032**	0.141
Miscellaneous	r	−0.533	−0.578	−0.437	−0.569	−0.359	−0.439	−0.607	−0.478
	p	*0.002**	*0.001**	*0.016**	*0.001**	*0.052**	*0.015**	*<0.001**	*0.008**
NMS total	r	−0.858	−0.836	−0.916	−0.904	−0.819	−0.811	−0.800	−0.813
	p	*<0.001**	*<0.001**	*<0.001**	*<0.001**	*<0.001**	*<0.001**	*<0.001**	*<0.001**

Abbreviations: BP, Bodily Pain; GH, General Health; MH, Mental Health; NMS, Non-Motor Symptoms; PF, Physical Functioning; RE, Role Emotional; RP, Role-Physical; SF, Social Functioning; VT, Vitality. $p < 0.05$: significant. $p < 0.001$: highly significant. Correlations by Pearson Correlation Coefficient; Italics values indicates significant of p values.

was a predictor of perceived intellectual well-being (mental health) ($\beta = 0.262$, $p = 0.040$) and general health ($\beta = -0.291$, $p = 0.030$), while sleep quality was a predictor of emotional role ($\beta = -0.224$, $p = 0.015$).

Comparison of NMSs between the younger and the older age groups

The patients and control were divided into two subgroups of younger age group (≤45 years of age, 14 patients and 17 controls) and older age group (>45 years of age, 16 patients and 13 controls), for further analysis of the impact of age. The mean age of the younger ET patients and controls were matched, 28.14 ± 8.22 and 29.71 ± 4.77 respectively ($p = 0.513$), and the mean age of the older ET patients and the controls were 60.13 ± 8.09 and 61.39 ± 8.62, respectively (matched, $p = 0.689$). The mean illness duration of the younger and the older ET patients were 8.00 ± 4.72 years and 12.50 ± 9.49 years, respectively, with no significant difference ($p = 0.119$). The mean FTM-TRS scores of the younger and the older ET patients were 38.43 ± 11.43 and 45.31 ± 15.2, respectively, with no significant difference ($p = 0.177$). All patients with comorbidities were among the older age group.

Compared to their matched controls, the younger ET patients showed significant cognitive impairment ($p = 0.021$) and a significance tendency for depression ($p = 0.056$), while older patients had more depression ($p = 0.009$), with no significant difference of cognitive impairment. PSQI in both groups showed no statistically significant differences. Regarding NMSS, the younger group showed significant differences in total NMSS and most of its domains, compared to younger controls, except urinary symptoms ($p = 0.136$), while the older group showed significant differences of total NMSS and most of its domains, except urinary, gastrointestinal, and perceptual symptoms ($p = 0.236$, 0.249, 0.181, respectively). Comparing patients' age-groups, older patients had more significant cognitive impairment ($p = 0.003$) and worse sleep/fatigue ($p = 0.032$) and sexual ($p = 0.006$) NMSS domains (Table 3).

ET patients showed statistically highly significant impairment (lower scores) on all QoL subscales compared to controls in both age groups (all $p < 0.001$, except general health in older group ($p = 0.022$)) (Table 3). Comparing two patients' age groups, there was no significant differences of QoL subscores except that mental health was worse among the older group ($p = 0.016$). Total NMSS of both age groups was correlated

Table 3. **Comparison of Neuropsychiatric Symptoms and NMS between ET Patients and Controls**

	Younger ET patients ≤ 45 years	Older ET patients 45 years	p*	Younger controls ≤ 45 years	p*	Older controls > 45 years	p*
Number	14	16		17		13	
Age	28.14 ± 8.22	60.13 ± 8.09	**<0.001**	29.71 ± 4.77	0.513	61.39 ± 8.62	0.689
MoCA	27.43 ± 2.59	24.25 ± 2.65	**0.003**	29.12 ± 1.11	**0.021**	25.15 ±1.41	0.277
BDI	12.43 ± 6.63	14.13 ± 5.49	0.450	8.23 ± 4.92	0.056	9.39 ± 2.96	**0.009**
PSQI	5.50 ± 2.10	6.69 ± 3.38	0.266	4.24 ± 2.93	0.187	4.62 ± 1.98	0.062
NMSS total	50.43 ± 14.18	64.69 ± 24.86	0.069	10.53 ± 7.38	**<0.001**	25.92 ± 10.87	**<0.001**
(1) Cardiovascular	3.79 ± 3.87	4.50 ± 3.43	0.596	0.06 ± 0.24	**<0.001**	2.23 ± 1.59	**0.037**
(2) Sleep/fatigue	8.07 ± 5.50	12.69 ± 5.87	**0.035**	3.53 ± 3.48	**0.009**	4.85 ± 3.56	**<0.001**
(3) Mood/cognition	16.43 ± 6.51	18.56 ± 8.64	0.457	4.65 ± 3.2	**<0.001**	6.46 ± 4.20	**<0.001**
(4)Perceptual problems	1.71 ± 2.46	1.06 ± 1.123	0.349	0	**0.007**	0.54 ± 0.88	0.181
(5)Attention/memory	6.29 ± 4.08	9.75 ± 5.63	0.067	1.18 ± 1.29	**<0.001**	5.00 ± 3.44	**0.013**
(6) Gastrointestinal symptoms	1.64 ± 2.47	1.38 ± 2.96	0.792	0	**0.01**	0.39 ± 0.65	0.249
(7) Urinary symptoms	0.64 ± 1.74	1.50 ± 2.00	0.224	0	0.136	0.77 ± 0.93	0.236
(8) Sexual function	2.86 ± 3.39	5.25 ± 3.32	0.006	0	**0.002**	1.23 ± 1.69	**<0.001**
(9) Miscellaneous	9.00 ± 5.41	10.00 ± 4.50	0.585	1.12 ± 2.23	**<0.001**	4.46 ± 2.90	**0.001**

Abbreviations: BDI, Beck Depression Inventory; MoCA, Montreal Cognitive Assessment; NMSS, Non-Motor Symptoms Scale; PSQI, Pittsburgh Sleep Quality Index; SD, Standard Deviation. $p < 0.05$: significant. $p < 0.001$: highly significant. *Compared by student's *t*-tests; Bold values indicates significant of p values.

to all QoL subscores (all $p < 0.001$, $p = 0.010$ for social functioning in the younger group), except mental health in the younger age group ($r = -0.451$, $p = 0.105$), with no significant correlation with patients' age, duration of illness, and tremor severity.

Discussion

Despite the previous several studies that confirmed the non-motor aspects of ET, further studies are needed to confirm their phenotypes in different populations and their correlation to disease severity and duration. The current study explored several NMSs associated with ET and detected their negative impact on QoL. These findings are comparable to other studies and confirm the importance of NMSs as an intrinsic component of ET for proper patient management.

In accordance with prior studies, patients with ET in the current study showed significant cognitive impairment, particularly of visuospatial/executive, naming and recall functions. Previous study reported consistent findings with similar impairment of visuospatial/executive and recall functions.[17] Similarly, the total MoCA score was impaired in Korean ET cohort, but dysfunction was significant in attention.[5] Also, other studies have reported the presence of mild cognitive deficits of frontal lobe functions similar to Parkinson's disease (PD), which was attributed to dysfunction of frontocerebellar circuits[18,19] and the increased risk of dementia in patients with ET.[20]

These cognitive functions are similarly affected in the cerebellar cognitive affective syndrome (CCAS), which was described in different cerebellar disorders by Hoche and colleagues. The CCAS is characterized by impairment of the executive, linguistic, visuospatial, and affective functions.[21] Also, cerebellar structural abnormalities were confirmed pathologically in ET, which were similar in early onset and late onset cases.[22] This indicates that cerebellum is implicated in the neuropathology of ET and associated cognitive dysfunction,[1] and supports the hypothesis that cognitive affection is a part of the disease pathology rather than an age-related symptom. In addition, this study found no significant correlation between MoCA scores and disease duration and tremor severity, similar to Sengul and his colleagues,[17] but in contrast to another study that detected correlation with tremor severity.[23]

Similar to the previous studies, patients with ET had significantly higher frequency and scores of depression, which was correlated to tremor severity.[7,24] These results were also consistent with a large door-to-door study using Hamilton Depression Rating Scale (HDRS).[25] In contrast, previous studies used the Geriatric Depression Scale (GDS) that reported significant depression with ET, but without correlation to tremor severity,[19,26] while a recent study detected non-significant difference in BDI.[9] These variable findings could be explained by using different depression scales and variable number of recruited ET patients, and

maintain the debate of the nature of depression as a reaction to the tremor or inherent part of the illness.

Likewise, ET patients have significantly more anxiety than matched controls, which was not correlated with age, age of illness onset, illness duration, or tremor severity. This was similar to the study performed by Chandran and his colleagues on patients from an outpatient clinic.[7] Other studies showed significantly higher anxiety in ET patients that was correlated with tremor severity.[25,27] Our findings support the hypothesis that anxiety is a part of ET and not a secondary phenomenon. However, other studies with different results keep the debate still open.[25,27]

The current study detected poor sleep quality of ET patients using PSQI, in agreement with previous studies.[7,28] Contrarily, another study compared the Epworth Sleepiness Scale (ESS) and the PSQI scores in 120 ET patients to controls and reported non-significant worse sleep quality.[29] Quality of sleep showed no correlation with age, age of illness onset, illness duration, or with tremor severity, implying that the problem of sleep regulation is an intrinsic part of ET.

Moreover, patients with ET reported significant impairment of all NMSS domains, especially sleep/fatigue, mood/cognition, and memory/attention domains, which showed limited correlations with patients' age, and tremor severity, comparable to the findings by Lee and his colleagues using similarly the NMSS. Consequently, this supports the hypothesis that non-motor manifestations are an intrinsic feature of ET.[8,9] Interestingly, similar non-motor profile was detected in Egyptian PD patients.[30] On the other hand, other previous studies used the non-motor symptoms questionnaire (NMSQuest) and/or compared patients of ET to PD patients. An epidemiological survey of Chinese populations reported NMSs among ET patients, similar to normal controls, except higher frequency of restless legs.[31] Compared to PD tremor dominant type, ET patients showed less NMSs, but with comparable severity,[32] while other studies reported more NMSs among PD patients than ET using NMSQuest.[33,34] Therefore, further case control studies with larger numbers are warranted to confirm the findings of the present study.

The current study confirmed the significant impairment of self-reported QoL in all sub-domains that were correlated with increased tremor severity. These findings are similar to those reported by Lorenz and his colleagues.[2] However, other studies reported that significant impairment of QoL was limited to mental domains – mental component score (MCS).[9,17] The German cohort showed no correlation for the impaired MCS; however, physical component score was negatively correlated to disease severity.[9] This difference could be attributed to higher severity of tremor of our outpatient clinic study compared to the German study that recruited patients through media. All QoL domains were negatively correlated to depression severity, similar to prior studies.[17,35] Likewise, anxiety was negatively correlated with physical functioning, mental health, role limitations due to physical health, and emotional problems, similar to a previous study.[17] In addition, the NMSS total score was significantly related to and a predictor of the overall well-being (physical, emotional and intellectual) for patients with ET. Moreover, perceived mental health and role-emotional subdomains of mental component of QoL were correlated to cognition and sleep quality, respectively. Few studies correlated QoL of ET with patients' cognition and sleep quality, with no significant findings.[9,17]

For further analysis of the impact of age, the cases and controls were classified into two age subgroups (≤45 and >45 years of age), with matched disease duration and tremor severity. Comparison to age-matched controls detected that both age groups showed significant NMSs with subsequent impairment on QoL. Both age groups with matched disease characteristics showed comparable non-motor features, except worse cognition and sexual functions among older ET patients. In the older age group, none of the neuropsychiatric or NMSS domains showed correlation with age, illness duration, or tremor severity except with that of sleep quality and fatigue. Consequently, non-motor features seem to be disease-associated rather than age-associated manifestations. Comorbidities might explain worse autonomic functions among the older patients; however, previous studies reported lack of this association, implying the need of further studies.[7,36]

The relatively small number of patients and the selection bias of patients and controls are the main limitations of the present study. Enrollment of matched controls regarding age, sex, and socioeconomic state was adopted to reduce selection bias. Patients enrolled from the outpatient clinic might be more disabled and had worse symptoms, in contrast to population-based studies, resulting in pursuing medical consultation. However, our findings were comparable with similar case–control studies of ET.[5,7]

Despite these limitations, the current study demonstrated that patients with ET presenting to clinics have several NMSs, including depression, anxiety, sleep disturbance, and cognitive dysfunction that impaired their QoL. Moreover, these non-motor features occur similarly in younger and older patients with minimal differences and are mostly integral part of ET regardless of tremor severity or patients' age. Consequently, better awareness and assessment of these symptoms result in better management of patients with ET. Also, further studies are required to explore the phenotypes and progression of these NMSs of ET patients in different populations.

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