Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Essential Tremor and Depression

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Abstract: **Introduction:** Depression and neuropsychiatric disorders in individuals with essential tremor (ET) are not well characterized in the literature.

Methods: We compared 104 ET subjects with 481 non-ET controls involved in the Arizona Study of Aging and Neurodegenerative Disorders. An analysis of baseline depression scales and neuropsychiatric inventory (NPI) was done between the two groups. Additionally, comparisons were made within the ET group based on tremor severity, duration of tremor, and age of onset.

Results: There were no significant differences between the ET and non-ET groups. There were no significant differences in the ET group above and below the median tremor duration. Additionally, no differences were found in the ET group based on objective measures of tremor severity, age of onset, or those with subjectively distressing tremor compared with those without.

Conclusion: There were no significant differences in depressive symptoms between ET and non-ET groups. Furthermore, no correlation was found between depressive symptoms in ET groups based on tremor severity, duration, or age of onset.

Essential tremor (ET) is the most prevalent movement disorder[1] with well-characterized motor symptomatology. However, non-motor manifestations of ET are being increasingly recognized in the literature.[2,3] Depression has been well studied in other common movement disorders, such as Parkinson's disease, but the role of psychiatric and mood disorders remains unclear in ET. One study reported that 5.4% of a community sample and 10.8% of a Movement Disorders Clinic sample met DSM-IV criteria for major depressive disorder. Another study comparing depression in various movement disorders found only 1.9% of the ET cases had "severe" depression using Beck's Depression Inventory and only 3.8% had "moderate to severe" depression.[4,5]

The purpose of this study was to determine if depression and neuropsychiatric symptoms are more prevalent in patients with ET compared with non-ET controls. Furthermore, we investigated whether these symptoms correlate with measures of disease severity, such as duration of ET or tremor amplitude. Since previous reviews have suggested subtyping ET based on age of onset,[6,7] we compared depression scales among subjects without ET and those with tremor onset prior to and after age 65 as well.

Methods

This study was conducted at the Arizona Study for Aging and Neurodegenerative Disorders (AZSAND), which began in 1997 and is based at Banner Sun Health Research Institute in Sun City, AZ. All subjects signed written informed consent approved by the Banner Sun Health Research IRB. Subjects were initially recruited into the study largely as a result of lectures and community awareness within the catchment area of Maricopa County, Arizona. All subjects, regardless of entering diagnoses, had annual assessments for Parkinson's disease, tremor, and other movement disorders at each visit including Fahn-Tolosa-Marin (FTM) tremor scale assessing postural, kinetic, head, and voice tremor performed by movement disorder specialists. Neuropsychiatric status was ascertained annually using Hamilton Depression Scale (HAM-D), Geriatric Depression Scale (GDS), and, beginning in 2006, the Neuropsychiatric Inventory (NPI).[8] Subjects were also assessed annually for cognitive status with standardized neuropsychological testing and annual consensus conference. Annual cognitive testing included: WAIS-III Digit Span, auditory verbal learning test (ReyAVLT),

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Keywords: essential tremor, depression, tremor, cognitive.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 17 March 2017; revised 23 June 2017; accepted 27 June 2017.
Published online 25 September 2017 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12530

doi:10.1002/mdc3.12530

controlled oral word association (COWAT), category fluency, Boston naming test (BNT), clock drawing, Judgement of Line Orientation (JLO), Trails Part A/B, STROOP, and MMSE. MCI was defined by modified Petersen criteria as previously described.[9] Subjects with Parkinsonism or dementia were excluded, as were subjects with restless leg syndrome.

Essential tremor was prospectively defined according to accepted criteria.[10–12] Participants were diagnosed with ET if they had a clinical diagnosis of ET[10] and the examination was consistent with that diagnosis or if they had an isolated head or voice tremor without dystonia. If the participants did not have a diagnosis of ET but did have a postural or kinetic hand tremor score of ≥2 on the FTM scale without secondary cause, then they were given a research diagnosis of ET. If the participants had a postural or terminal tremor of the hands <2, they were categorized as having tremor NOS. These participants were then reclassified as ET on subsequent annual examinations if they had persistent tremor greater than 3 years without secondary cause. Controls were defined identically to ET other than they lacked tremor in annualized assessment.

In order to assess rate of neuropsychiatric symptoms in relationship to ET severity, four analyses were done within the ET group. Those with subjectively distressing tremor were compared to those without. Subjectively distressing tremor was defined as a UPDRS Part II tremor score >1. Tremor duration was also used as a surrogate of tremor severity and so the neuropsychiatric scales were compared between those above and below the median tremor duration. These two groups were also compared with controls. Subjects with early onset and longer duration tremor were compared to subjects with later onset and shorter duration by using Cox regression. Early onset was defined as tremor onset prior to age 65 years as suggested by previous reviews.[6] Lastly, the ET group was divided into two groups above and below the median tremor amplitude as measured by the sum of the components of the FTM scale for postural, kinetic, head and voice tremor.

Statistical Analyses

Demographics and diagnosis were summarized and compared between the ET and non-ET groups using Chi-square test or two-sample t-test when appropriate. Comparison of GDS, HAMD, and NPI total severity scores by different groups was done using ANCOVA method by adjusting for gender and age at baseline. NPI subscales between ET and non-ET groups were compared using Chi-square test or Fisher's exact test when applicable.

Results

Using the AZSAND database, 585 subjects met criteria for analysis of which 104 were in the ET group and 481 were controls. The ET group was more likely to be male (55.8% vs. 33.9%) and older (80.7 years vs. 77.2 years) compared with controls (Table 1). Mean age of tremor onset was 66.0 years ± 21.4 and mean duration of tremor was 14.7 years. The median age of onset for the group was 73.5 years. There were no differences in mild cognitive impairment between ET and non-ET groups. In the ET group, the median, mean (SD), and range FTM scores were 5, 5.5,[3] and 0 to 17. Of these patients, 13% had grade 3 or more tremors in a body part indicating more severe tremor. Due to low numbers, these patients' results were not separately analyzed.

TABLE 1 Demographics and diagnosis summary by ET

	ET (N = 104)	Non-ET (N = 481)	Total (N = 585)	*p*-value
Female				0.0001
No	58 (55.8%)	163 (33.9%)	221 (37.8%)	
Yes	46 (44.2%)	318 (66.1%)	364 (62.2%)	
Age at Baseline				0.0001
N	104	481	585	
Mean (SD)	80.7 (6.7)	77.2 (8.4)	77.8 (8.3)	
Median	81.0	78.0	79.0	
Range	(50.0-99.0)	(32.0-99.0)	(32.0-99.0)	
CON Cognitive Status				0.2343
NL	96 (92.3%)	423 (87.9%)	519 (88.7%)	
MCI	8 (7.7%)	58 (12.1%)	66 (11.3%)	
Treatment for depression from Medical History				0.2196
Missing	57	302	359	
Never	30 (63.8%)	135 (75.4%)	165 (73.0%)	
Past	4 (8.5%)	14 7.8%)	18 (8.0%)	
Now	13 (27.7%)	30 (16.8%)	43 (19.0%)	
Tremor duration				
N	104	–	–	
Mean (SD)	14.7 (19.8)	–	–	
Median	6.1	–	–	
Range	(0.0-83.8)	–	–	
Age at Tremor Onset				
N	104	–	–	
Mean (SD)	66.0 (21.4)	–	–	
Median	73.5	–	–	
Range	(0.0-90.0)	–	–	

doi:10.1002/mdc3.12530

TABLE 2 Comparison of GDS, HAMD and NPI total severity score between ET and non-ET groups[1]

Variable	ET (N = 104)	Non-ET (n = 481)	Diff. (95% CI)	P value	Effect Size
Geriatric Depression Scale (0-30); adjusted mean (SE), N	4.2 (0.42), 103	3.8 (0.19), 470	0.4 (-0.5 to 1.3)	.38	0.10
HAM-D; adjusted mean (SE), N	3.7 (0.32), 91	3.2 (0.15), 393	0.5 (-0.2 to 1.2)	.19	0.14
NPI Total Severity Score; adjusted mean (SE), N[2]	1.6 (0.39), 43	1.7 (0.20), 164	−0.1 (-0.9 to 0.8)	.88	0.02

[1]Gender and age at baseline were adjusted in the comparison.
[2]Among the subset people who had NPI (n = 207).

There was no statistically significant difference in GDS, HAM-D, and NPI total severity scores between ET and non-ET groups (Table 2). There were also no differences in the NPI positive measures between the two groups, including scores for depression, anxiety, apathy, or irritability (Table 3). While more subjects in the ET group seemed to be previously or currently treated for depression based on medical history, this difference did not reach statistical significance (Table 1).

Within the ET group, 26 subjects reported UPDRS part II tremor score of 0, 47 subjects reported tremor score 1, and 31 reported tremor score >1. Amongst these subjects, there was no significant difference reported in GDS ($p = 0.70$), HAM-D ($p = 0.52$), and NPI total severity scores ($p = 0.55$).

Depression and neuropsychiatric assessment scores were also reviewed within the ET group above (n = 53) and below (n = 51) median tremor duration of 6 years. There was no statistical difference in GDS ($p = 0.32$), HAM-D ($p = 0.18$), and NPI total severity scores ($p = 0.54$). The mean FTM score for tremor duration less than 6 years was 4.8 ± 2.2 with a median score of 5.0. The mean FTM score for tremor duration greater than 6 years was 6.1 ± 3.5 with median score of 6.0. These two subgroups, based on tremor duration, were also compared to 481 non-ET controls and no significance was noted in GDS ($p = 0.42$), HAM-D ($p = 0.17$), and total NPI scores ($p = 0.88$).

The ET group's neuropsychiatric scores were compared based on the median FTM scale of 5, with sample size of 52 in both groups. For FTM > 5: GDS, HAM-D, and NPI total severity scores mean and SE were 3.9 (0.60), 3.5 (0.45), 1.6 (0.45) respectively. For FTM ≤ 5: GDS, HAM-D, and NPI total severity scores mean and SE were 4.6 (0.59), 3.7 (0.45), 1.8 (0.46) respectively. No statistically significant differences were noted in GDS ($p = 0.40$), HAM-D ($p = 0.82$), and NPI total severity ($p = 0.75$).

There was no statistical difference in GDS, HAM-D, and NPI total severity scores amongst groups with tremor onset prior to age 65, at or later than age 65, and those without ET (Table 4).

TABLE 3 NPI positive measures by ET

	No (N = 164)	Yes (N = 43)	Total (N = 207)	*p*-value
NPI Total Positive				0.3121
No	79 (48.2%)	17 (39.5%)	96 (46.4%)	
Yes	85(51.8%)	26 (60.5%)	111 (53.6%)	
NPI-Q Delusions				1.0000
No	162 (98.8%)	43 (100.0%)	205 (99.0%)	
Yes	2 (1.2%)	0 (0.0%)	2 (1.0%)	
NPI-Q Hallucinations				NA
No	164 (100.0%)	43 (100.0%)	207 (100.0%)	
NPI-Q Agitation or Aggression				0.6647
No	138 (84.1%)	35 (81.4%)	173 (83.6%)	
Yes	26 (15.9%)	8 (18.6%)	34 (16.4%)	
NPI-Q Depression or Dysphoria				0.6330
No	128 (78.0%)	35 (81.4%)	163 (78.7%)	
Yes	36 (22.0%)	8 (18.6%)	44 (21.3%)	
NPI-Q Anxiety				1.0000
No	150 (91.5%)	40 (93.0%)	190 (91.8%)	
Yes	14 (8.5%)	3 (7.0%)	17 (8.2%)	
NPI-Q Elation or Euphoria				1.0000
No	163 (99.4%)	43 (100.0%)	206 (99.5%)	
Yes	1 (0.6%)	0 (0.0%)	1 (0.5%)	
NPI-Q Apathy or Indifference				0.0827
No	145 (88.4%)	42 (97.7%)	187 (90.3%)	
Yes	19 (11.6%)	1 (2.3%)	20 (9.7%)	
NPI-Q Disinhibition				0.3594
No	152 (92.7%)	38 (88.4%)	190 (91.8%)	
Yes	12 (7.3%)	5 (11.6%)	17 (8.2%)	
NPI-Q Irritability or Liability				0.7937
No	114 (69.5%)	29 (67.4%)	143 (69.1%)	
Yes	50 (30.5%)	14 (32.6%)	64 (30.9%)	
NPI-Q Motor Disturbance				0.2096
No	156 (95.1%)	43 (100.0%)	199 (96.1%)	
Yes	8 (4.9%)	0 (0.0%)	8 (3.9%)	
NPI-Q Nighttime Behaviors				0.8547
No	128 (78.0%)	33 (76.7%)	161 (77.8%)	
Yes	36 (22.0%)	10 (23.3%)	46 (22.2%)	
NPI-Q Appetite and Eating				0.0989
No	151 (92.1%)	36 (83.7%)	187 (90.3%)	
Yes	13 (7.9%)	7 (16.3%)	20 (9.7%)	

Discussion

Essential tremor is a common movement disorder with a prevalence of 4.6% in patients 65 years and older.[13] While the motor symptoms have been well documented and characterized, there is conflicting data on the presence of non-motor symptoms.[2,10] In this current study, essential tremor is not associated with a higher prevalence of depression or other neuropsychiatric symptoms compared to non-ET controls. Furthermore, duration of tremor, severity of tremor based on amplitude, and subjectively distressing tremor were not associated with an increase in the GDS, HAM-D, or total NPI scores. Subjects with ET were more likely to be currently or previously treated for depression but this finding did not reach clinical significance.

Previous studies have suggested that there are significant psychosocial variables that are more prevalent in ET patients. In regards to the pathophysiology of these previous findings, some authors have suggested that ET may be a primary neurodegenerative process, implicating the cerebello-thalamo-cortical

doi:10.1002/mdc3.12530

TABLE 4 Comparison of GDS, HAMD and NPI total severity score among groups with tremor onset before age 65, at or after age 65, and non-ET group

Variable	Non ET (N = 481)	Tremor onset age < 65 (N = 29)	Tremor onset age ≥ 65 (N = 75)	*p*-value
Geriatric Depression Scale (0-30); adjusted mean (SE), N	3.8 (0.19), 470	3.3 (0.77), 29	4.6 (0.49), 74	.23
HAM-D; adjusted mean (SE), N	3.2 (0.15), 393	3.0 (0.58), 27	4.0 (0.38), 64	.18
NPI Total Severity Score; adjusted mean (SE), N	1.7 (0.20), 164	1.0 (0.65), 15	2.0 (0.48), 28	.47

pathway, which would explain neuropsychiatric manifestations.[14] The findings in this study do not suggest an inherently higher prevalence of depressive symptoms in patients with ET, arguing against the concept that depression may be pathologically phenotypic of ET. ET has been proposed to be a heterogeneous disorder, specifically familial with younger ages of onset versus non-familial.[15] More studies are needed to elucidate the potential of neurodegeneration in ET and if this is relevant to specific subgroups.

Alternatively, it has been hypothesized that depression and changes in quality of life may be secondary to the disability produced by ET, but the data from multiple analyses continue to be limited in support of this.[16–18] In the current study, mood dysfunction was not associated with tremor severity or tremor duration, supporting that depression may not be a secondary function of disability in this cohort. This study is limited in that it reviewed indirect measures of the functional impact of tremors rather than a self-reported assessment of the neuropsychiatric influences of tremor. Additionally, while the treatment of depression in the ET group was not significantly higher than the non-ET group, the treatment itself may have impacted GDS and HAM-D in the ET group impacting the comparative analyses of these measures.

The patients recruited for the AZSAND study tend to belong to an overall retired community. The impact of work related disability might be lower in this population potentially explaining why we did not find a correlation between depressive symptoms and patient disability. The population studied was also older but it should be noted that more than 50% of ET patients are reported to have an age of onset greater than 70 years.[19] These subjects were also drawn from the community rather than a clinic population which may be more disabled and, therefore, more likely to be depressed. As the understanding of ET evolves and it is increasingly characterized as a heterogeneous disease, it becomes important to elucidate subsets within the ET population. Although the AZSAND study population is homogenous, it is a well-characterized group. Strengths of this study include the longitudinal, prospective study of both subjects with ET and controls being assessed in identical manner. Additionally, the inclusion of more mildly affected individuals allows one to address an earlier phenotype that might better assess non-motor features before significant disability develops.

Our study does not support previous findings linking ET to depression neither as part of a primary non-motor syndrome with specific depressive characteristics[20] nor as a finding related to the tremor severity, which would theoretically correspond to disability. However, since other groups have found a correlation between ET and depression, it is recommended providers screen all patients for signs of depression.

Acknowledgements

We are grateful to the subjects who have volunteered to participate in the Banner Sun Health Research Institute Brain and Body Donation Program. The authors thank Mr. Bruce Peterson for developing and maintaining the database.

Author Roles:

1. Research Project: A. Conception B. Organization C. Execution; 2. Statistical Analysis: A. Design B. Execution C. Review and Critique; 3. Manuscript Preparation: A. Writing of the First Draft B. Review and Critique.

S.A.: 1A, 1B, 1C, 2A, 2C, 3A, 3B
N.Z.: 2A, 2B, 3B
C.A.: 1C, 1A, 2C, 3B
J.C.: 1C, 3B
E.D.D.: 1C, 3B
S.H.M.: 1C, 3B
M.S.: 1C, 3B
C.B.: 1C, 3B
E.Z.: 1C, 3B
T.B.: 1C, 3B
H.A.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3B

Disclosures

Funding Sources and Conflicts of Interest: The Arizona Study of Aging and Neurodegenerative Disorders is supported by the National Institute of Neurological Disorders and Stroke (U24 NS072026 National Brain and Tissue Resource for Parkinson's Disease and Related Disorders), the National Institute on Aging (P30 AG19610 Arizona Alzheimer's Disease Core Center), the Arizona Department of Health Services (contract 211002, Arizona Alzheimer's Research Center), the Arizona Biomedical Research Commission (contracts 4001, 0011, 05-901, and 1001 to the Arizona Parkinson's Disease Consortium), The Michael J. Fox Foundation for Parkinson's Research, the Mayo Clinic Foundation, Sun Health Foundation, Bob and Renee Parsons Foundation, and the International Essential Tremor Foundation. The authors declare that there are no conflicts of interest relevant to this work.

doi:10.1002/mdc3.12530

Financial Disclosures for previous 12 months: Dr. Aslam has no disclosures. Ms. Zhang has no disclosures. Dr. Adler has received consulting fees from Acadia, Adamas, Cynapsus, Impax, Ipsen, Jazz, Lundbeck, Merz, and Neurocrine. Dr. Caviness has received grants from The Michael J. Fox Foundation for Parkinson's disease research. Dr. Driver-Dunckley has received research support from Ipsen, EMD Sereno, Abbvie, BMS, and The Michael J Fox Foundation. Dr. Mehta has received research grants for clinical trials from Acorda Therapeutics, Cynapsus Inc., US WorldMeds, and is an investigator for SURE PD3 through the Parkinson's Study Group. Dr. Sabbagh has consulted for Axovant, Biogen, Grifols, Humana, Lilly Pharmaceuticals, Sanofi, and vTv Therapeutics. He has received research grants from AstraZeneca, Avid Pharmaceuticals, Axovant, Genentech, Inc., Lilly Pharmaceuticals, Merek & Co, Pfizer, Roche Diagnostics Corporation, vTv Therapeutics, and Piramal Imaging. He is a stock shareholder in Brain Health, Muses Labs, and Versanum. Dr. Belden receives clinical trial funding support from AbbVie, Neuronix, Astra Zeneca, Novartis, Avanir, Avid, Axovant, Biogen, Genentech, IntraCellular, Lilly, Merck, Roche, Suven, Takeda, and inVentiv Health; also, Arizona Alzheimer's Consortium, Sun Health Foundation, NIH, and CMS. Dr. Zamrini receives clinical trial funding support from AbbVie, Acadia, Neuronix, Astra Zeneca, Novartis, Avanir, Avid, Axovant, Biogen, Genentech, IntraCellular, Lilly, Merck, Otsuka, Roche, Suven, Takeda, NeuroEM, and inVentiv Health; also, Arizona Alzheimer's Consortium, Sun Health Foundation, NIH, and CMS. Dr. Beach has served on an advisory boards for Genentech and consultant for GE Healthcare and Avid Radiopharmaceuticals. He has research support from Avid Radiopharmaceuticals, Navidea Biopharmaceuticals, The Michael J Fox Foundation, NIH, and the Arizona Department of Health and Human Services. Dr. Shill has served as a consultant with Cynapsus/Sunovion, Abbvie, and Lundbeck. Dr. Shill has received research support from Cynapsus/Sunovion, Axovant, Impax, US World Meds, The Michael J. Fox Foundation, and the NIH.

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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doi:10.1002/mdc3.12530