Anxiety spectrum disorders are common in patients with orthostatic tremor

D.E. Bhatti a, R.J. Thompson a, K. Malgireddy a, N.M. Syed a, B. Bayer b, D. Bessette b, M.H. Fleisher b, D.L. Murman a, D. Torres-Russotto a,⁎

a Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, Nebraska, United States of America
b Department of Psychiatry, University of Nebraska Medical Center, Omaha, Nebraska, United States of America

ABSTRACT

Background: Orthostatic Tremor (OT) is a rare movement disorder characterized by a sensation of unsteadiness while standing and associated with high frequency tremors. Patients with OT commonly report a fear of falling and significant limitations in everyday activities. The prevalence of psychiatric comorbidities in OT patients has not been well-studied.

Methods: Subjects were evaluated by trained psychiatry researchers using the Mini International Neuropsychiatric Interview (M.I.N.I.). The M.I.N.I is a validated screening tool for psychiatric disorders. A standardized history covering previous psychiatric symptoms and illnesses was also obtained.

Results: 29 OT subjects were evaluated. The mean age was 67.7 years with female preponderance (89.3%). The average disease symptom duration was 18.2 years. 58.6% of the subjects had seen a mental health professional during the course of their OT illness. 24.1% of the subjects had a past history of depression, and 10.3% reported a family history of any psychiatric condition. 37.9% of the subjects screened positive for agoraphobia. Two of 29 subjects (6.9%) were classified as having a current major depressive episode and one subject (3.4%) was at risk for suicide.

Conclusions: Psychiatric comorbidities are highly prevalent in OT patients, especially anxiety-spectrum disorders. Further studies are needed to understand if psychiatric disorders appear as a secondary response to the patient's symptoms, or are a primary non-motor manifestation of OT.

1. Background

OT is a rare disorder of marked unsteadiness with high frequency tremors of the lower extremities that occurs while standing and is relieved by walking, sitting or leaning against objects. It was first comprehensively described by Pazzaglia et al. in 1970 [1], and coined as OT by Heilman in 1984 [2]. In 1998, the Movement Disorder Society in a consensus statement on tremors, provided a concrete definition of OT (Table 1) [3]. A number of retrospective studies have been reported. The condition is more common in females (65–80% female), and onset is usually in middle age. There is an associated action tremor in the upper limbs in about two thirds of patients [4–6].

Patients with OT often report a fear of falling and significant limitations in everyday activities. It is particularly difficult for them to wait in lines, stand at a cashier, and perform the daily activities requiring standing like taking a shower, washing dishes or cooking. Playing sports that intermittently require a stance position (like tennis, golf, and baseball) are difficult. Although these patients are exposed to significant levels of stress and suffering, the prevalence of psychiatric comorbidities in OT patients is not well understood. Retrospective studies have shown a possible increase in mood and anxiety disorders [4]. A single previous neuropsychiatric study found that OT patients have statistically significant higher mean scores for anxiety related disorders and depression, as well as borderline and antisocial features [7]. Multiple medications with possible cognitive side effects are frequently administered to OT patients. Recently thalamic DBS has been shown to yield sustained benefit in selected patients with medically refractory orthostatic tremor [8].

The ascertainment of psychiatric comorbidities in people with OT has clear clinical and therapeutic implications. In this study we prospectively explored the psychiatric comorbidities in OT using a validated detailed screening tool.

2. Methods

2.1. Participants

Subjects with known primary OT diagnoses previously confirmed with surface EMG as per MDS taskforce diagnostic criteria [3] were prospectively enrolled. Participants were part of the University of Nebraska Medical Center (UNMC) OT Study, a prospective comprehensive OT cohort.

http://dx.doi.org/10.1016/j.prdoa.2019.07.001
2590-1125/© 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Subjects from USA, Canada, Europe and Australia participated in the study. All of the subjects were native English speakers. This protocol was approved by the UNMC Institutional Review Board. Informed consent was obtained from all subjects.

2.2. Procedure

After obtaining informed consent, a detailed history was obtained using a standardized patient intake form and a comprehensive neurological exam was performed. Subjects were then interviewed by psychiatry researchers using the Mini-International Neuropsychiatric Interview (M.I.N.I.) to screen for major psychiatric disorders. The M.I.N.I. has been thoroughly validated, and has reliability scores that compared well to other structured psychiatric interviews like the SCID-P and CIDI [9]. It is used to screen for major categories of psychiatric disorders such as depression, anxiety disorders, phobias, psychosis and other mood disorders. The M.I.N.I. is divided into several diagnostic modules. Each module has screening questions corresponding to the criteria of a single disorder. At the end of each module, the clinician indicates whether diagnostic criteria are met.

With regards to the question about seeing a mental health professional in the past, the question was worded as: ‘Have you seen or talked to a mental health professional such as a psychiatrist, psychologist of a psychiatric nurse about your own health in the past?’ This did not include any counseling visits.

3. Results

34 subjects were screened, of which 5 patients were excluded due to being unavailable for interview or declining participation. The rest of the 29 patients with surface-EMG-confirmed primary OT were included in the study. All 29 patients completed the M.I.N.I. interview. The mean age was 67.8 years, and 89.3% of subjects were female with 18 years of average disease duration and 9 years since diagnosis.

Results of our standardized history are summarized in Table 1. During the interview, 58.6% (17/29) of patients reported that they had seen a mental health professional in the past. 24.1% of the patients reported a past history of depression, and 10.3% had a family history of any psychiatric condition. In terms of history of substance abuse, 3.4% of the participants had a previous smoking history, 6.9% reported a history of alcohol abuse, and 17.2% reported they used illegal/street drugs in the past.

Results of the M.I.N.I are listed in Table 2. 37.9% (11/29) of the OT patients screened positive for agoraphobia while, 6.9% (2/29) screened positive for a major depressive episode and for panic disorder. The two subjects who screened positive for panic disorder also had screened positive for agoraphobia and one of these two subjects had previously been diagnosed with social phobia. One of the subjects screened positive for generalized anxiety disorder and one other subject for current suicide risk.

4. Discussion

OT patients commonly report a sense of impending fall on standing and this has been associated with a significant fear of falling, even though the majority of these patients rarely fall. In this study we explored the psychiatric comorbidities of OT and found a high incidence of anxiety-spectrum disorders. These patients are constantly scanning their environment to see where they could sit down, or hold onto something to avoid the sensation of an impending fall.

The significance of this fear of falling is not fully understood. In OT, it is unclear if the tremor causes the sensation of instability, or if the sensation of instability causes the tremor, or if both result from an epiphenomenon. It has previously been shown that inducing unsteadiness in normal subjects, by vestibular galvanic stimulation or by leaning backwards, can cause the subjects to develop a fast tremor in the lower extremities [10]. This suggests that OT could be an exaggeration of a physiological response to perceived instability. There have been multiple studies concluding that anxiety can disrupt the vestibular system enough to induce dizziness [11,12]. A critical issue is to determine if the anxiety secondary to basiphobia (fear of standing) can induce tremors similar to those seen in patients with OT.

A previous study did suggest that anxiety related disorders are more common in OT patients compared to controls but the data was not classified into specific anxiety disorders [7]. Two previous studies have shown that there is an increased prevalence of depression in OT when compared to the general population and to controls [4,7]. However, in our relatively large study, we did not find a high prevalence of depression (6.9% of the OT subjects screened positive which is similar to the general population of the USA) [13].

The interviews revealed an unexpectedly high proportion of OT patients screening positive for phobias (agoraphobia and social phobia). Agoraphobia is a type of anxiety disorder that involves intense fears and often avoidance of places from which it would be hard to escape. Agoraphobia in our subjects was significantly higher at 37.9% compared to 0.8% in the general population [13]. The high rate of agoraphobia reported could directly be related to the fear of developing OT symptoms when having to stand in large crowds. A limitation of our study is that we did not attempt to clarify if agoraphobia preceded the presence of OT symptoms as this particular instrument does not inform us on the time of onset of any of the conditions. Furthermore, we could not correlate symptom severity of OT to presence of agoraphobia. At the time that this data was collected, there was not a single validated scale to measure the severity of OT. As part of the study, we did collect subjective information but this has not been properly validated to be used as a marker of presence nor of severity of the disease.

In our cohort, 6.9% of subjects in the study screened positive for panic disorder which is high compared to the general population in the USA (2.75%) [13]. The etiology for this is unclear but this could be a reflection of the OT patients’ suffering and the limitations on their activities of daily living (a secondary basiphobia in response to OT). Moreover, agoraphobia is a situation-specific phobia that could be induced or aggravated by the typical symptoms in OT. Secondly, it could be that patients with OT have intrinsically higher risk for phobic disorders as discussed earlier. In fact, OT could be viewed in this case as a phobia of standing associated with high-frequency tremors. Thirdly, there is a possibility that OT and phobias

| Table 1: Standardized history-intake results. |
|-----------------------------------------------|
| History                                      |
| Past history of depression                    |
| Current smoking                               |
| Previous smoking                              |
| Currently drinking alcohol                    |
| Past alcohol abuse                            |
| Previous illegal/street drugs                 |
| Family h/o psychiatric conditions             |
| Positive (%) n = 29                           |
| 7 (24.1%)                                    |
| 0 (0%)                                        |
| 1 (3.4%)                                      |
| 17 (58.6%)                                    |
| 2 (6.9%)                                      |
| 5 (17.2%)                                     |
| 3 (10.3%)                                     |

| Table 2: Patients who screened positive in the M.I.N.I. |
|--------------------------------------------------------|
| Conditions                                              |
| No. of patients who responded positive (%) n = 29       |
| Suicide risk current                                    |
| Major depressive episode, current                       |
| Generalized Anxiety Disorder, current                   |
| Prevalence in the general population (%) USA population |
|                                                       |
| Have you ever seen a mental professional?               |
| 17 (58.6%)                                               |
| 2 (6.9%)                                                 |
| 1 (3.4%)                                                 |
| 1 (3.4%)                                                 |
| 4.8-9.2% [18]                                           |
| 6.7% [13]                                               |
| 4.3% [19]                                               |
| 0.8% [13]                                               |
| 2.75% [13]                                              |
| 7.1% [20]                                               |
| 2.7% [21]                                               |

a Mini-International Neuropsychiatric Interview.

b The source separates the statistics for those with mental insurance (9.2%) and those without (4.8%).

c In the past year.
are both epiphenomena of a different, singular pathophysiological mecha-
nism. We do admit that this result could be due to an intrinsic problem
with our screening tool that would render the M.I.N.I. unable to discern
phobias from OT symptoms.

There are several other limitations of this study. Firstly, 10.3% of the pa-
tients reported a positive psychiatric family history, although, according the
data reported by the NIMH, an estimated 31.1% of adults in the US ex-
perience any anxiety disorder in their lifetime, and the prevalence of any
mental illness of US adults is quoted as 19.1% [14]. The question was
worded as, ‘Do you have any family member(s) with psychiatric disorders?’
We believe the reason behind this to be multifactorial including lack of
knowledge of a family member’s psychiatric diagnosis, recall bias, and
other biases. Finally, we did not separate drug abuse or dependency from
‘any use’.

OT is a rare disease and therefore recruitment of large numbers is chal-
 lenging. In fact, the UNMC OT study is one of the largest prospective studies
for this disorder. Importantly, subject participation requires traveling, and
this produces a recruitment/selection bias. A control group was not in-
cluded for this arm of the study because the M.I.N.I. is a well-characterized
screening tool. However, to put the findings into perspective we can com-
pare the rates of psychiatric co-morbidities with those in PD. The percent-
age of panic disorder that we found (6.9%) is similar to that in Parkinson’s
disease (PD) patients [15]. However, the suicidal risk of 3.4% was consider-
ably less than that in PD (11.2%) [16]. Similarly the percentage
of patients with major depression (6.9%) is significantly less than seen in
PD (17%) [17].

In conclusion, the prevalence of anxiety disorders in OT is signifi-
cantly high compared to the general population. Panic disorder and agoraphobia
were especially prevalent in OT suggesting a relationship to the situation-
specific symptoms experienced by this population and might be significant
non-motor manifestations of OT and a possible etiopathogenic association.

Conflict of interest

Bhatti DE: Dr Bhatti has been consultant and/or speaker for Accadia,
Merz, Allergan, Teva Neurosciences, Adamas, Abbvie and Allergan Paki-
stan. Dr. Bhatti has nothing to disclose related to this study. • Thompson
R: No conflicts of interest. • Malg ireddy K: No conflicts of interest. • Syed
NM: No conflicts of interest. • Bayer B: No conflicts of interest. • Bassette
D: No conflicts of interest. • Fleisher MH: No conflicts of interest. • Murman
DL: University of Nebraska Medical Center receives support for Dr. Murman
and his team to conduct clinical trials related to Alzheimer’s disease at
UNMC, including some “percent effort” support of Dr. Murman’s salary.
These trials include the following pharmaceutical companies; Eli Lilly &
Co., Novartis, and Roche. Dr. Murman also receives some salary support
from NIH-funded research. These research projects and financial support
are not related to the content of this manuscript. • Torres-Russotto D: Dr.
Torres-Russotto has been a speaker and/or consultant for: AbbVie, Acorda,
Adamas, Allergan, Ipsen, Lundbeck, Teva, Sunovion.

References

{[1] P. Pazzaglia, L. Sabattini, E. Lugaresi, On an unusual disorder of erect standing position
(observation of 3 cases), Rivista sperimentale di freniatria e medicina legale delle
alienazioni mentali, 94 (2) (1970) 450–457.
[2] K.M. Heilman, Orthostatic tremor, Arch. Neurol. 41 (8) (1984) 880–881.
[3] G. Deuschl, P. Bain, M. Brin, A.H.S. Committee, Consensus statement of the movement
disorder society on tremor, Mov. Disord. 13 (S3) (1998) 2–23.
[4] W. Genschler, A. Münchau, R. Katzschschläger, P. Brown, J.C. Rothwell, N. Quinn, A.J.
Lees, K.P. Bhatia, Natural history and syndromic associations of orthostatic tremor: a re-
view of 41 patients, Mov. Disord. 19 (7) (2004) 788–795.
[5] P.C. McManis, F.W. Sharbrough, Orthostatic tremor: clinical and electrophysiologic
characteristics, Muscle & Nerve: Official J. of the Am. Assoc. of Electrodiagnostic
Med. 16 (11) (1993) 1254–1260.
[6] P. Pihlouml, Q.P. Yu, S.L. Pullman, Clinical and neurophysiologic spectrum of ortho-
static tremor: case series of 26 subjects, Movement Disorders: Official J of the Mov. Dis.
Soc. 20 (11) (2005) 1455–1461.
[7] J. Benito-León, E.D. Louis, V. Puerta-Martín, J.P. Romero, M. Matarazzo, J.A. Molina-
Arjona, C. Domínguez-González, A. Sánchez-Ferro, Cognitve and neuropsychiatric fea-
tures of orthostatic tremor: a case-control comparison, J. Neurol. Sci. 361 (2016) 137–143.
[8] A. Merosa, A. Fasano, A. Hassan, J.L. Ostrem, M.F. Contarino, M. Lyons, J.K. Krauss, M.
E. Wolf, B.T. Klassen, A.F. van Rooijen, I. Regidor, A.P. Duker, W. Ondo, J. Guridi, J.
Volkmann, A. Wagle Shakya, G.T. Mandybur, M.S. Okun, K. Witt, P.A. Starr, G. Deuschl,
A.J. Espay, Thalamic deep brain stimulation for orthostatic tremor: A multicenter inter-
national registry, 32(8) (2017) 1240–1244.
[9] D.V. Sheehan, Y. Leckhuber, K.H. Sheehan, P. Amorim, J. Janavs, E. Weiller, T. Hergueta,
R. Baker, G.C. Dunbar, The Mini-International Neuropsychiatric Interview (MINI): the
development and validation of a structured diagnostic psychiatric interview for DSM-
IV and ICD-10, The J. of clinical psychiatry 23 (Suppl 20) (1998) 22–199.
[10] A. Sharott, J. Marsden, P. Brown, Primary orthostatic tremor is an exaggeration of a
physiological response to instability, Movement Disorders: Official Journal of the Move-
ment Disorder Society 18 (2) (2003) 195–199.
[11] J.P. Staab, C.D. Babahan, J.M. Furman, Threat assessment and locomotion: clinical ap-
plications of an integrated model of anxiety and postural control, Seminars in Neurology
Thieme Medical Publishers (2013) 297–306.
[12] C.M. Goehlo, C.D. Babahan, Viscuo-vestibular contributions to anxiety and fear, Neurosci.
Biobehav. Rev. (48) (2015) 148–159.
[13] R.C. Kessler, W.T. Chin, O. Demler, E.E. Walters, Prevalence, severity, and comorbidity
of 12-month DSM-IV disorders in the National Comorbidity Survey Replication, Arch.
Gen Psychiatry 62 (6) (2005) 617–627.
[14] T.N.L.M. Health, Any Anxiety Disorder, https://www.nimh.nih.gov/health/statistics/
any-anxiety-disorder.shtml (2017).
[15] M.P. Broen, N.E. Narayen, M.L. Kujif, N.N. Disanayaka, A.F. Leentjens, Prevalence of
anxiety in Parkinson’s disease: a systematic review and meta-analysis, Mov. Disord.
31 (8) (2016) 1125–1133.
[16] S. Naeem, A.D. Siderowf, J.E. Duda, G.K. Brown, T. Ten Have, M.B. Stern, D. Weintraub,
Suicidal and death ideation in Parkinson’s disease, Movement Disorders: Official Jour-
nal of the Movement Disorder Society 23 (11) (2008) 1573–1579.
[17] J.S. Reijnders, U. Ehrt, W.E. Weber, D. Aarsland, A.F. Leentjens, A systematic review of
prevalence studies of depression in Parkinson’s disease, Movement Disorders: Official
Journal of the Movement Disorder Society 23 (2) (2008) 183–189 (quiz 313).
[18] T.N.L.M. Health, QuickStat percentage of adults aged 18–64 years who have seen or
talked with a mental health professional in the past 12 months, * by health insurance
status and age group — National Health Interview Survey, United States, 2012–2013,
https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6408a10.htm#s_cid =
mm6408a10_w64(07) (2017) 197.
[19] T.N.L.M. Health, Suicide, https://www.nimh.nih.gov/health/statistics/suicide.shtml
(2019).
[20] T.N.L.M. Health, Social Anxiety Disorder, https://www.nimh.nih.gov/health/statistics/
social-anxiety-disorder.shtml#part_1559022017.
[21] T.N.L.M. Health, Generalized anxiety disorder, https://www.nimh.nih.gov/health/
statistics/generalized-anxiety-disorder.shtml 2017.