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Anxiety spectrum disorders are common in patients with orthostatic tremor

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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.

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Table 1
Standardized history-intake results.

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

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 MINI 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.

Table 2
Patients who screened positive in the M.I.N.I.[a]

Conditions	No. of patients who responded positive (%) n = 29	Prevalence in the general USA population (%)
Have you ever seen a mental professional?	17 (58.6%)	4.8–9.2%[b] [18]
Major depressive episode, current	2 (6.9%)	6.7% [13]
Suicide risk current	1 (3.4%)	4.3% [19]
Agoraphobia	11 (37.9%)	0.8% [13]
Panic disorder with Agoraphobia, current	2 (6.9%)	2.75% [13]
Social phobia	1 (3.4%)	7.1%[c] [20]
Generalized Anxiety Disorder, current	1 (3.4%)	2.7%[c] [21]

[a] Mini-International Neuropsychiatric Interview.
[b] The source separates the statistics for those with medical insurance (9.2%) and those without (4.8%).
[c] In the past year.

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

are both epiphenomena of a different, singular pathophysiological mechanism. 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 patients reported a positive psychiatric family history, although, according the data reported by the NIMH, an estimated 31.1% of adults in the US experience 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 challenging. 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 included 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 compare the rates of psychiatric co-morbidities with those in PD. The percentage 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 considerably less than that in PD (11.2%) [16]. Similary 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 significantly 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 Pakistan. Dr. Bhatti has nothing to disclose related to this study. • Thompson R: No conflicts of interest. • Malgireddy K: No conflicts of interest. • Syed NM: No conflicts of interest. • Bayer B: No conflicts of interest. • Bessette 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.

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