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Balance and cognitive impairments are prevalent and correlated with age in presurgical patients with essential tremor

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ABSTRACT

Introduction: Essential tremor (ET) was long considered a monosymptomatic disorder, but this view has given way to a more comprehensive clinical picture that involves consideration of non-tremor symptoms (e.g., balance impairment, cognitive impairment). Recently, the novel designation of "ET-plus" was proposed to reclassify ET patients who demonstrate these non-tremor clinical features, but the prevalence of ET-plus remains poorly defined. The primary aim of our study was to estimate the prevalence of ET-plus among presurgical patients with ET by applying this reclassification scheme.
Methods: We performed a retrospective review of patients with ET being considered for deep brain stimulation or focused ultrasound thalamotomy. Patient demographics and data from their clinical workups were collected. As part of their clinical workup, patients were screened for preexisting balance and cognitive impairment. Patients with ET were designated as ET-plus if they had balance impairment, cognitive impairment, or tremor at rest. We performed a series of Pearson correlations to examine how individual clinical and demographic variables were related.
Results: We identified 92 patients who met the study criteria. Our results indicate that 87% of the presurgical patients in our cohort met the criteria for reclassification as ET-plus. In addition, we observed robust correlations between patient age and balance impairment, cognitive impairment, history of falls, family history of tremor, and ET-plus reclassification.
Conclusion: We propose that balance and gait impairment should be assessed preoperatively alongside neuropsychological evaluation to improve the counseling and treatment of patients with ET-plus.

1. Introduction

Essential tremor (ET) is among the most common neurological disorders in the world, with a higher prevalence than Parkinson's disease or Alzheimer's disease [1]. The characteristic feature of ET is a 4- to 12-Hz kinetic tremor, most often in the upper extremities, that interferes with activities of daily living, such as eating, writing, and dressing. Tremor may also affect the head, voice, face, and lower limbs. In cases of severe refractory tremor, a range of surgical approaches aimed at destruction or inhibition of the thalamus, typically the ventral intermediate nucleus, have been used successfully [2–4].

ET has long been considered a monosymptomatic disorder, but this view has given way to a more comprehensive clinical picture that involves consideration of non-tremor symptoms [5]. Of these non-tremor symptoms, cognitive impairment, balance impairment, and gait disturbances are frequently observed [6–9]. To capture the heterogeneous clinical presentation of ET patients, a recent reclassification of the disorder as two distinct phenotypes, ET and ET-plus, has been proposed—the latter denoting ET patients who present with impaired balance, impaired cognition, tremor at rest, or other neurological signs of

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unknown clinical significance [6].

Since its inception, the new classification has prompted critical discussion, with some arguing that we should instead consider ET a family of diseases [7–9]. Notably, early efforts to apply this new classification to existing patient cohorts have suggested that ET-plus may be more common than ET [10,11], although the prevalence of ET-plus remains poorly defined. Given emerging evidence that the presence of ET-plus features influences the outcome of thalamic surgery [12,13], greater efforts to apply this classification scheme are warranted, particularly for presurgical patients.

To this end, our primary aim was to estimate the prevalence of ET-plus among presurgical patients with ET by retrospectively applying this reclassification scheme. We hypothesized that examination of balance and cognitive impairment in our presurgical cohort of patients with ET would lead to a very frequent reclassification of the patient as ET-plus. Moreover, we anticipated a strong association between ET-plus status and age, given the greater risk for balance and cognitive impairment observed among patients generally with advanced age [14].

2. Methods

2.1. Patients

The medical records of patients considered for deep brain stimulation or focused ultrasound thalamotomy were examined to document tremor severity, tremor-related disability, cognitive impairment, and balance disorders. Only those patients with a primary diagnosis of ET who were evaluated between 10/2018-06/2021 were included in the study. The clinical workup included a detailed patient history, which provided information about comorbid health conditions, history of falls, and family history of ET. We collected patient demographic data and the results of the clinical workup from the patient's electronic medical record; the study was approved by the University of Utah institutional review board.

2.2. Presurgical workup

The presurgical workup typically included a comprehensive evaluation of balance and tremor by a licensed physical therapist (J.B.). The Berg Balance Scale (BBS) [15,16] was used to assess balance and fall risk because it is easy to perform in the clinic and applies to an older population of adults. Other measures of balance and gait that were measured included the Romberg test, single limb stance, and tandem gait test. Tremor type and severity were measured using the Fahn-Tolosa-Marin tremor rating scale [17]. Many patients were administered the Montreal Cognitive Assessment (MoCA) [18] to screen for cognitive impairment.

2.3. Statistical analyses

All statistical analyses were performed using SPSS (Version 26; Chicago, IL, USA). A "combined balance metric" was created as a binary variable (0 = unimpaired, 1 = impaired) to simplify the analysis of balance impairment. A patient was designated with balance impairment if they had one or more of the following: history of falls, impaired Romberg test (<30 s) [19], impaired single limb stance (<5 s with eyes open) [20], impaired tandem gait stance (<10 s) [21], or "high risk" designation on the BBS (≤44) [15]. Cognitive impairment was defined as MoCA <26. In line with the proposed reclassification, patients with ET were designated as ET-plus if they had balance impairment, cognitive impairment, or tremor at rest. We performed a series of Pearson correlations to examine how individual clinical and demographic variables were related.

3. Results

Ninety-two patients with ET (67 male, 72.8%) had a balance workup, MoCA evaluation, or both, although some lacked scores for all measures because of loss to follow-up and evaluations scheduled beyond the time at which data was collected. (Table 1). The mean age of our cohort was 73.5 ± 8.9 years (range 43–90). A family history of tremor was reported in 54/86 (62.8%) patients. A previous history of falls (31/86, 36.0%) or a high-risk BBS score (21/82, 25.6%) was less common; however, 52/86 (60.5%) patients failed one or more balance tests. We observed some degree of resting tremor in 59/84 (70.2%) of the patients in our cohort. Of the 69 patients with a MoCA score, 42 (60.9%) met the criteria for mild cognitive impairment (MoCA < 26). The mean BBS and MoCA scores for the patients in our cohort were 48.5 (*SD* = 7.0) and 24.1 (*SD* = 3.8), respectively.

After quantifying the degree of balance impairment, cognitive impairment, and resting tremor in our cohort, we concluded that 87.0% of the patients in our cohort (80/92) met the criteria for reclassification.

Analysis of the relationship between age and other clinical variables of interest revealed several robust associations (Table 2, Fig. 1). As expected, advanced age was positively correlated with the combined balance metric ($r(84) = 0.291$, $p < .01$) and history of falls ($r(86) = 0.249$, $p < .05$) and negatively correlated with MoCA score ($r(69) = -0.318$, $p < .01$) and family history of tremor ($r(86) = -0.310$, $p < .01$). There was a strong positive correlation between ET + reclassification and age ($r(84) = 0.362$, $p < .001$).

At the time of analysis, 58/92 (63%) of the patients in our cohort received either FUS (n = 54) or DBS (n = 4) for the treatment of tremor. Of the 34 (37%) of patients who had not yet received surgery, a small number of patients opted out of surgery or were determined ineligible (n = 3), some had scheduled a date for surgery in the future (n = 8), and most were either pending completion of their presurgical evaluation or undecided about treatment (n = 23).

4. Discussion

4.1. ET-plus reclassification

The vast majority (87.0%) of presurgical ET patients in our cohort met the criteria for ET-plus. Although few estimates for the prevalence of ET-plus exist, our findings align with previous studies, which suggest that ET-plus is more common than ET [10,11]. Our observed prevalence is higher than has been reported previously, but this may be due to our focus on presurgical patients who present with more severe clinical symptoms than ET patients generally.

It is also possible that the advanced age of our cohort may partially explain this high prevalence of ET-plus because age was strongly associated with both balance and cognitive impairment. However, age-matched comparisons between patients with ET and healthy controls

Table 1
Demographic and clinical features of 92 pre-surgical ET patients.

Variable	Value (N = 92)
Age *(in years, mean ± SD)*	73.5 (8.9)
Sex *(no. male, %)*	67 (72.8%)
Balance & tremor evaluation	(N = 86)
Family history of tremor (no., %)	54 (62.8%)
History of falls *(no. with 1 + falls, %)*	31 (36.0%)
History of multiple falls (no. with > 1 falls, %)	20 (23.3%)
Romberg test *(no. impaired, %)*	12 (14.3%)
Single limb stance *(no. impaired, %)*	47 (56.6%)
Tandem gait *(no. impaired, %)*	7 (8.3%)
Berg balance scale *(no. high risk, %)*	21/82 (25.6%)
Combined balance metric *(no. impaired, %)*	52 (60.5%)
Resting tremor *(no., %)*	59/84 (70.2%)
Neuropsychiatric evaluation	(N = 69)
Montreal Cognitive Assessment *(no. impaired, %)*	42/69 (60.9%)

Table 2
Pearson correlation matrix for demographic and clinical features of interest.

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	–												
2. Sex†	0.034	–											
3. Family hx of tremor	-0.310**	-0.046	–										
4. Hx of falls	0.249*	-0.137	-0.174	–									
5. Hx of multiple falls	0.211	-0.2	-0.146	0.733**	–								
6. Romberg test‡	0.104	-0.079	0.03	0.193	0.349**	–							
7. Single limb stance‡	0.300**	-0.118	-0.022	0.233*	0.402**	0.342**	–						
8. Tandem gait‡	0.085	-0.025	-0.037	-0.135	-0.060	-0.123	0.003	–					
9. BBS	-0.202	0.094	0.108	-0.434**	-0.604**	-0.695**	-0.665**	0.174	–				
10. Combined balance‡	0.291**	-0.072	-0.081	0.260*	0.445**	0.328**	0.928**	0.243*	-0.603**	–			
11. Resting tremor	0.171	-0.135	-0.12	0.105	0.165	0.191	0.061	0.196	0.118	0.116	–		
12. MoCA	-0.318**	-0.237	0.014	-0.116	-0.095	-0.029	-0.159	-0.218	0.045	-0.210	-0.019	–	
13. ET+	0.362**	0.054	-0.247*	0.157	0.176	0.123	0.347**	0.091	-0.239*	0.396**	0.463**	-0.134	–

Hx: History, BBS: Berg Balance Scale, MoCA: Montreal Cognitive Assessment.
* = $p < .05$.
** = $p < .01$.
† = sex was binarized (male = 1, female = 0).
‡ = outcome was binarized (impaired = 1, normal = 0).

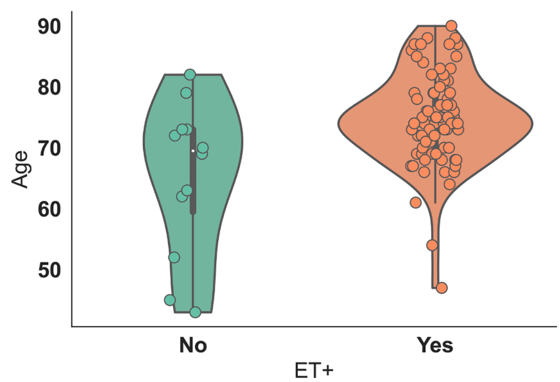

Fig. 1. Distribution of age among presurgical ET patients classified by whether the patient was redesignated as ET + after evaluation.

provide evidence for a unique, albeit poorly understood, contribution of ET pathophysiology to balance and cognitive impairment. For example, one study which separately analyzed those of advanced age (≥70 years) reported that patients with ET were significantly more likely than age-matched controls to have tandem gait abnormalities (71.4% vs. 22%) [22]. Similarly, others have reported that, although age covaries with many gait and balance measures, activities-specific balance confidence is significantly lower in patients with ET than age-matched controls of advanced age (≥70 years) [23]. Large, population-based studies provide additional support for a relationship between ET and cognitive impairment; mild cognitive impairment was more common among patients with ET (20.3%) than age-matched controls (16.1%) [24]. Notably, these patients would meet criteria for ET-plus reclassification, however the studies predate the use of the ET-plus designation [6].

Critically, certain ET-plus features have been shown to meaningfully influence surgical outcome. One recent study reported ataxia among a higher number of patients with ET who developed early tolerance to stimulation of the ventral intermediate nucleus of the thalamus [13]. Similarly, although it is unknown why some patients develop dystonia in response to thalamic surgery, some reports suggest it may be more common in those with pre-existing dystonic features [12]. These findings highlight the importance of presurgical screening for ET-plus features, particularly among patients of advanced age, to determine the best candidates for surgery.

4.2. ET and balance

In our cohort of patients with ET undergoing surgical workup, we observed a high prevalence of balance impairment. These findings are in line with previous studies, which have reported a higher prevalence of balance and cognitive impairment in ET patients than is observed in healthy older adults [22,24]. For example, approximately half of ET patients struggle during the tandem walk test [25,26], and ET patients report a lower level of confidence in their balance [23].

To assess balance, we reviewed performance on the BBS, a 14-item test consisting of various functional movements (e.g., bending over, sitting unsupported). Other clinical and quantitative assessments of balance exist and may be considered more comprehensive [27]; for example, the Balance Evaluation Systems Test [28] includes actions designed to isolate six different balance control systems (e.g., anticipatory postural adjustments, sensory orientation) in the presence of external perturbation. Using more comprehensive assessments of balance may help clinicians to identify and differentiate impairments in specific balance systems, but a lengthy battery of tests is more difficult to perform clinically, especially with an older population and is, therefore, better suited to assess balance impairment in younger adults.

Additionally, a robust relationship between ET and gait disturbance has been reported in the literature [26], but this was not explored at length in this study. A wide range of gait analysis methods exist [29], and subsequent testing may yield a richer understanding of the interaction between balance, gait, and cognitive function in ET patients and cast light on the shared mechanisms that underlay the observed impairment. However, the exact mechanistic relationship that underlies the association between balance impairment and cognitive decline in ET patients remains unclear.

4.3. ET and cognitive impairment

The relationship between ET and cognitive impairment has been previously explored through a large population-based study, the results of which indicate that patients with older-onset ET (after age 65) are 57% more likely to have mild cognitive impairment than age-matched controls [24]. Subsequent research on ET patients identified a robust relationship between cognitive decline and balance impairment, linking the number of falls and low balance confidence with diminished performance on tests of executive function, memory, and attention [30]. Given that various cognitive tests to detect impairment and dementia are available [31], future analyses should explore whether declines in specific cognitive abilities (e.g., visuospatial reasoning, executive function, orientation) are more informative than basic tools for screening patients like the MoCA.

4.4. Limitations

One significant limitation in our study is the inherent ambiguity behind the criteria for ET-plus. At present, unequivocal criteria do not exist. Instead, the criteria employ more fluid concepts like "other neurological signs of unknown significance" [6]. We attempted to simplify this reclassification scheme by using quantifiable metrics for balance and cognitive impairment for our analyses. However, this approach could be improved in several ways. First, the assessment of balance impairment likely favored sensitivity over specificity, given our use of a composite metric. In addition, other patient features that may merit ET-plus reclassification (e.g., dystonia) were not included in our analyses. Similarly, we chose not to collect or analyze additional demographic or clinical information from our patient cohort. Although we recognize that such information may provide a richer understanding of the patients and their comorbidities, we chose to focus our analyses on what was most pertinent to the ET-plus reclassification.

Our analyses were performed on a cohort of presurgical ET patients from a single institution and require further validation in larger samples. Moreover, presurgical patients typically present with severe tremors and may therefore not be representative of all ET patients. Thus, there may be an element of selection bias associated with the patient cohort. Finally, because these analyses were retrospective in nature, we were unable to evaluate the longitudinal effects of early cognitive decline on the subsequent development of balance impairment, which could serve as a meaningful prognostic tool with the potential to guide clinical decision-making.

5. Conclusions

Our data suggest a high prevalence of ET-plus reclassification in presurgical ET patients. We propose that balance and gait impairment should be assessed preoperatively alongside neuropsychological evaluation to improve the counseling and treatment of ET patients.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JDR is a consultant for Corlieve and Medtronic, unrelated to the study. The other authors have no conflicts of interest.

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