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Tandem gait abnormality in Parkinson disease: Prevalence and implication as a predictor of fall risk

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ABSTRACT

Introduction: We report the prevalence of abnormal tandem gait (TG) in patients with idiopathic Parkinson disease (PD) and its association with symptoms of subjective unsteadiness, falls, freezing of gait, and cognitive impairment.

Methods: We assessed subjective balance impairment, fall history, antero-posterior postural instability, and TG in PD patients (Hoehn and Yahr (HY) stage 0–4). We recorded the age, sex, current medications, HY stage, Schwab and England (S&E) scale score, and MOCA score for each patient. Logistic regression was used to evaluate age-adjusted associations between TG and other demographic and clinical factors.

Results: A total of 102 patients with PD were assessed. Of those, 63.5% of HY 2 patients and 100% of HY 2.5 and 3 patients had a TG abnormality. The presence of TG abnormality was associated with subjective imbalance, falls, freezing of gait, S&E $<$ 80, and MOCA score $<$ 24 after adjustment for age.

Conclusions: TG abnormality is common in PD, precedes the development of antero-posterior postural instability, is associated with cognitive impairment, and may predict fall risk. A longitudinal study will help determine if TG is a predictor of impending progression from HY 2 to HY 3.

1. Introduction

Parkinson disease (PD) is characterized by its core motor features of bradykinesia, rigidity, and rest tremor [1]. As PD progresses, patients develop antero-posterior postural instability (APPI) as detected by the pull test [2]. The presence of this abnormality defines the transition from Hoehn and Yahr (HY) stage 2 to stage 3^2 and is associated with increased disability due to high risk for falls. Tandem gait (TG) testing is an integral part of the neurological exam, and can be informative in a wide variety of disorders including cerebellar disease, vestibular and peripheral neuropathies, and neurodegenerative conditions [3]. Classically, mediolateral balance impairment as measured by TG testing has been considered a “red flag” pointing towards an underlying atypical parkinsonism (AP) [4,5]. However, the prevalence of TG abnormality in patients with idiopathic PD has not been systematically studied. TG testing is not part of the standard PD motor assessment, the Movement Disorder Society-United Parkinson Disease Rating Scale (MDS-UPDRS), or the diagnostic criteria for PD. In this study we assessed the prevalence of TG abnormality in patients with PD and its association with subjective symptoms of unsteadiness, falls, freezing of gait, and cognitive impairment.

2. Materials and methods

This cross-sectional study included 102 consecutively recruited adult patients with PD representing all HY stages, who presented for a first-time evaluation and enrolled in an ongoing PD registry at the University of Miami Movement Disorders Clinic. PD was defined by UK PD Society Brain Bank Criteria [6]. We excluded patients with clinically apparent peripheral sensory neuropathy, concurrent vestibular pathology, gait impairing orthopedic abnormality, excessive alcohol use or AP. We assessed for large fiber neuropathy by examining vibration and proprioceptive senses in each patient as well as Romberg testing. AP was defined as clinically probable multiple system atrophy, progressive supranuclear palsy or dementia with Lewy Bodies per most recently published diagnostic criteria [7–9]. Patients with available brain MRI that was suggestive for vascular parkinsonism were also excluded.

Our study protocol assessed subjective balance impairment, fall history, freezing of gait history, APPI, and quantified TG abnormality in

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PD patients. We used relevant sections from the UPDRS and MDS-UPDRS for the subjective assessments, recording the patient's response to MDS-UPDRS question 2.12 (walking and balance), and from the UPDRS questions 13 (falling, unrelated to freezing) and 14 (freezing with walking)— each with a defined 0 to 4-point scale. Additionally, we recorded the age, sex, current medications, HY stage, Schwab and England Scale (S&E) and Montreal Cognitive Assessment (MOCA) score for each patient. At time of assessment, patients were either medication naïve, thus without motor or nonmotor fluctuations, or were in a medication ON state. All examinations were performed by experienced movement disorders specialists (JM, CS, HM, CL).

To test TG, patients were asked to walk heel-to-toe for 10 consecutive steps with their arms at their sides and eyes open. Patients were allowed two trials, and the best performance was scored—as defined by the relevant sections of the United Huntington's Disease Rating Scale (UHDRS) and the Scale for the Assessment and Rating of Ataxia (SARA). The UHDRS provides a 0–4 scoring system: 0 = normal TG for 10 steps, 1 = 1 to 3 deviations in 10 steps, 2= > 3 deviations, 3 = cannot complete 10 steps, and 4 = cannot attempt the exam. The Gait portion of the SARA scale is a 0 to 8-point scale. Scores 0 to 2 are relevant to TG; 0 = up to 1 misstep in 10, 1 = slight gait difficulties noted in completing 10 TG steps, and 2 = cannot complete 10 TG steps. A score of 1 or more in either scale was counted as abnormal TG. Postural instability was defined by the pull test (MDS-UPDRS 3.12). Patients were asked to take a comfortable stance were forewarned about the impending pull, and were pulled backwards from their shoulders with the intent to take them off balance. The response was scored 0 to 4; 0 = recovers with 1 or 2 steps, 1 = recovers in 3–5 steps, 2 = recovers in more than 5 steps, 3 = would fall if not caught, and 4 = loses balance spontaneously or with gentle pull. The best of 2 attempts was scored.

Descriptive statistics were summarized as mean and standard deviation (SD) for continuous variables and frequency for categorical variables. The comparisons between normal and abnormal TG patients were conducted for continuous variables using t-tests, and for categorical variables using chi-square tests, or Fisher exact tests if the variable had a category of 0 frequency. Logistic regression models were used to evaluate the age-adjusted associations of demographic and clinical factors with TG. A P value of (0.05 was considered statistically significant.

3. Results

Patient characteristics and study results are summarized in Tables 1 and 2. We included 102 patients in the study, 41 women and 61 men, ranging from age 36–85 years. Duration of disease ranged from 3 months to 27 years; with a mean of 5.27 years. The sample included 16 HY 1 patients, 63 HY 2 patients; 12 HY 2.5 patients, 9 HY 3 patients and 2 HY 4 patients. Among all HY stages, 65.6% had abnormal TG. Five HY 1 patients (31.3%) and 49 HY 2 patients (63.5%) had a TG abnormality. Of these HY 2 patients, 42.5% had a TG severity > 1 in the relevant sections of the SARA or UHDRS scales. All (100%) of HY stages 2.5, 3 and 4 patients had an abnormal TG exam. Increasing age had a statistically significant association with an abnormal TG ($p < 0.0001$), corresponding to an OR of 1.1 per year increase in age ($p = 0.0002$). A HY stage greater than 2 had a statistically significant association with an abnormal TG ($p < 0.0001$); with an OR of 25.59 ($p = 0.001$). Increased disease duration was also found to have significant association with abnormal TG ($p < 0.003$); the average disease duration of a patient with normal TG was 3 ± 2.5 years. We did not find a significant association between comorbid diabetes mellitus, the use of cholinesterase inhibitors, or the use of anticholinergic agents and abnormal TG.

Aspects of the MDS-UPDRS motor exam were compared in patients with normal and abnormal TG. We considered that symmetry versus asymmetry in the motor exam could affect TG. In our cohort 81% of patients had an asymmetric score in the lower extremities in terms of rigidity, bradykinesia or tremor. Of patients with a normal TG (34), 29 (85.3%) had an asymmetric exam. No correlation was found between the presence of an asymmetric motor exam and the presence of abnormal TG. Interestingly, higher overall rigidity score correlated significantly with abnormal TG ($p = 0.036$).

We assessed the patients' subjective experiences with gait and their association with TG testing. Of the 102 patients, 56 (54.9%) patients reported subjective unsteadiness, and of those, 43 (76.8%) had an abnormal TG exam (a significant association; $p = 0.0049$). Of the total, 28 patients (27.5%) reported a history of falling; 26 of those (92.8%) had an abnormal TG exam ($p = 0.0006$). Of the total, 27/102 patients (26.5%) reported freezing of gait; 26 (96.3%) of those had an abnormal TG exam ($p = 0.0009$). Odds ratios for detecting abnormal TG given a history of subjective unsteadiness, falling, or freezing of gait were calculated to be 3.43 ($p = 0.0109$), 6.86 ($p = 0.0046$), and 8.55 ($p = 0.0073$), respectively.

Out of the 102 patients, 15 had Schwab and England Scale < 80, which implies that the patient is not fully independent for activities of daily living. A score < 80 was found to be significantly associated with detecting an abnormal TG on exam ($p = 0.003$). A score of ≥80 had an OR of 0.11 ($p = 0.0166$) for detecting an abnormal TG.

Cognitive function was evaluated in all patients using the MOCA. Including all 102 patients, the mean MOCA score was 24 ± 5. Of patients with a normal TG exam, the mean MOCA score was 26 ± 2 (range 21–30); of those with an abnormal TG exam, the mean score was 23 ± 6 (range 7–30). Overall, 36/102 patients (35.3%) scored < 24 out of a maximum score of 30 on the MOCA. Of these 36 individuals, 30 (83.3%) had an abnormal tandem gait. Lower MOCA scores were significantly associated with abnormal TG exam ($p = 0.0018$). For each 1 point higher than the mean MOCA score, a reduction of 12% in the odds of detecting an abnormal TG was observed.

4. Discussion

Abnormal TG is common in patients with PD, and was seen in almost two-thirds of our cohort including all HY stages. Abnormal TG is seen in conditions that extend beyond cerebellar dysfunction, including PD and AP, Huntington disease (HD), peripheral neuropathies, and vestibulopathies [3]. TG abnormality is also seen in aging adults without associated neurologic signs or symptoms. Bragin et al. reported that 71 of 391 (18.1%) healthy participants over age of 65 years had an isolated TG abnormality [4]. Abnormal TG in PD and AP (and likely in HD) suggests mediolateral balance impairment, which may be seen earlier in AP compared to PD and is attributed to extranigral lesions. Pathology may involve the cerebellum, cerebellar pathways, brainstem nuclei, and/or subcortical white matter, and is often with associated MRI abnormalities. Peripheral pathology, as in neuropathy or vestibulopathy, can also cause an abnormal tandem gait exam. A normal gait, including capacity to walk in tandem, requires that multiple systems, both neurologic and musculoskeletal, are able to function normally and in concert.

Early mediolateral balance involvement has been considered a “red flag” for AP [10–12]. Abdo et al. reported on 36 patients with PD and 49 patients with AP [11] that, 92% of patients with PD had a normal TG exam (defined as taking not a single side step in 10 consecutive tandem steps), whereas 82% of patients with AP had an abnormal TG exam. Thus, TG was considered useful in differentiating PD from AP. Aerts et al. report a similar association [10]. Their study included 110 patients, 61 with AP and 49 with PD. Of all clinical parameters studied, TG performance proved best for differentiating between AP and PD, with an area under the curve of 0.81 ($p < 0.0001$). TG was assessed using the relevant section of the International Cooperative Ataxia Rating Scale (ICARS).

Conversely, Lindholm et al. (2016) assessed a model to predict risk of falls in PD patients combining TG assessment with retropulsion testing and a history of falls or near falls [13]. To assess TG, participants

Table 1
Sample characteristics in PD patients with normal and abnormal TG.

	All (N = 102)		Normal TG (N = 34)		Abnormal TG (N = 68)		p-value
Age (yr) Mean ± SD	68 ± 10		62 ± 10		71 ± 9		< 0.0001
Disease Duration (yr) Mean ± SD	5.3 ± 4.8		3 ± 2.6		6.4 ± 5.4		< 0.003
Sex, n(%)							1.0000
F	42	41.2	14	41.2	28	41.2	
M	60	58.8	20	58.8	40	58.8	
HY stage, n(%)							< 0.0001
1	16	15.7	11	32.4	5	7.4	
2	63	61.8	23	67.6	40	58.8	
2.5	12	11.8	0	0	12	17.6	
3	9	8.8	0	0	9	13.2	
4	2	1.9	0	0	2	3.0	
LED (mg) Mean ± SD	374 ± 378		266 ± 269		430 ± 415		0.156
Subjective unsteady, n(%)							0.0049
No	46	45.1	22	64.7	24	35.3	
Yes	56	54.9	12	35.3	44	64.7	
Walking unbalanced, n (%)							0.2409
No	23	22.5	10	29.4	13	19.1	
Yes	79	77.5	24	70.6	55	80.9	
History of falling, n (%)							0.0006
No	69	67.6	31	91.2	38	55.9	
Yes	33	32.4	3	8.8	30	44.1	
History of freezing, n (%)							0.0009
No	75	73.5	32	94.1	43	63.2	
Yes	27	26.5	2	5.9	25	36.8	
S & E score, n (%)							0.0030
< 80	15	14.7	0	0.0	15	22.1	
80+	87	85.3	34	100.0	53	77.9	
MOCA score, Mean ± SD	24 ± 5		26 ± 2		23 ± 6		0.0018

Legend: LED: Levodopa Equivalent Dose.

Table 2
Association of demographic and clinical factors with TG abnormality after adjustment for age.

	%, abnormal TG	OR (95% CI)[a]	p-value[a]
Age, per year increase	N/A	1.10 (1.05–1.16)	0.0002
Sex			0.7183
F	66.7	Ref	
M	66.7	1.19 (0.47–2.98)	
HY stage			
< 2	31.3	Ref	
2	63.5	2.72 (0.70–11.85)[b]	0.1741
> 2	100.0	25.59 (4.34-infinity)[b]	0.0010
Subjective unsteady			0.0109
No	52.2	Ref	
Yes	78.6	3.43 (1.33–8.86)	
Walking unbalanced			0.1315
No	56.5	Ref	
Yes	69.6	2.22 (0.79–6.27)	
History of falling			0.0046
No	55.1	Ref	
Yes	90.9	6.86 (1.81–26.02)	
History of freezing			0.0073
No	57.3	Ref	
Yes	92.6	8.55 (1.78–41.08)	
S & E score			0.0166
< 80	100.0	Ref	
80+	60.9	0.11 (0.00–0.55)[b]	
MOCA score per unit increase	N/A	0.88 (0.77–1.00)	0.0523

[a] Model was adjusted for age.
[b] Estimates were based on exact logistic regression.

were instructed to take ten consecutive heel-to-toe steps along a straight line without walking aids or support, and with eyes open. A score of 0–3 was given: 0 (no side steps), 1 (1 side step), 2 (multiple side steps), or 3 (unable to take four consecutive steps). A score of 1 or more was deemed an abnormal TG performance. The study included 138 patients with PD; of these, 57% were found to have a TG abnormality. At 6-month follow up, the odds ratio (OR) of an abnormal TG at initial testing predicting future fall was 4.06 ($p < 0.01$).

Compared with previous reports, our cohort had a higher prevalence of abnormal TG with 65.7% of all patients, 63.5% of HY 2 patients, and 100% of HY 2.5 and 3 patients having an abnormal TG detected. Though assessed post-hoc, our results also suggest a strong association between TG abnormality and falling, as 92% of patients with a history of falls also had an abnormal TG assessment. Based on our findings, we propose that medio-lateral balance impairment is common in early stage PD and its presence does not suggest an AP. Despite its conspicuous absence from the UPDRS and MDS-UPDRS, TG has value in the assessment of patients with PD as a fall risk predictor and possibly as a predictor of impending disease progression.

The reasons for the discrepancy between our findings and previous publications are not obvious. Similar TG testing parameters and a similar definition of abnormal TG were employed by Abdo et al. [11] Aerts et al. used the International Cooperative Ataxia Rating Scale (ICARS) to rate TG abnormality. On this scale, TG is part of the assessment of “posture and gait disturbance,” however, the exact definition of an abnormal TG is not provided. The characteristics of our cohort are different from the patients described by Abdo et al. and Aerts et al. The cohort in Abdo et al. had a median age of 57.5 years, median disease duration of 2.5 years, and mean SE score of 80%. The cohort of Aerts et al. had a median age of 56.6 years and median disease duration of 2 years. The median age and disease duration in our cohort were 68 years and 5.27 years, respectively. Also we found that lower SE scores (less than 80%) were significantly correlated with a higher likelihood of TG abnormality. The older age, longer disease duration, and differences in functional status (as defined by the SE scale) may have contributed to the discrepant findings.

The breadth of motor and non-motor features in PD is a testament to nigral and extranigral pathology and PD can be viewed as a multisystem disorder [14,15]. To exemplify, non-motor features of constipation and cognitive decline, can be attributed to pathology in the dorsal motor nucleus of the vagus nerve and the nucleus basalis of Meynert, respectively [14]. Aspects of the gait abnormality in PD can be attributed to pathology in the pedunculopontine nucleus and premotor cortex

[14]. In PD, more widespread pathology—beyond the basal ganglia—likely underlies abnormal TG [3]. Cognitive and motor neural systems must work in concert for normal ambulation. Up to 40% of patients with PD meet criteria for mild cognitive impairment (MCI) [16]. Yarnall et al. reported MCI in 42.5% of their cohort of newly diagnosed PD patients [17]. The presence of MCI and Alzheimer's disease confer increased fall risk in older adults [18,19]. Thus, quality of cognition may be related to the ability to perform normal TG. In patients with essential tremor, abnormal TG performance correlates with cognitive dysfunction [20]. Verlindena et al. investigated the association between cognition and gait (including TG) in community dwelling adults over age 65 years [21]. Cognitive assessment included tests of memory, processing speed, fine motor speed, and executive function. Mini Mental Status Exams were performed on all participants. Of the domains tested, TG abnormality was only found to correlate with fine motor speed. In our cohort, on average, patients with abnormal TG had a MOCA score below 24. Overall, 35.3% patients fell into this range. This score range has a sensitivity of 100% and 83.3% in detecting amnestic and multi-domain MCI, respectively [22].

The significance of abnormal TG in PD patients is not fully understood. Abnormal sensory motor integration and central processing of proprioceptive input have been documented in PD patients and were proposed to be a result of supplemental motor area (SMA) dysfunction [23]. Impaired cerebellar sensory processing also plays an important part in PD and it is possible that increased cerebellar activity (either compensatory or pathological) may be responsible for abnormal TG as it is for PD related tremor [24,25]. Future studies are needed to clarify if impaired TG is a reflection of abnormal central proprioceptive processing, peripheral proprioceptive deficits, cerebellar dysfunction, or a combination.

Limitations to this study include its cross-sectional design and relatively small sample size without age matched controls. We did not perform objective balance measurements, but did use standardized validated scales for assessment. Peripheral neuropathy is prevalent in patients with PD, with large fiber neuropathy reported in 16.3% of 1376 patients, and small fiber neuropathy in 56.9% of 72 patients [26]. We do not have electrophysiologic evidence against subclinical neuropathy, but clinically apparent neuropathies were excluded. The pull-test, though performed by experience movement disorder specialists, is difficult to perfectly standardize from patient to patient. In the future, more in-depth neuropsychiatric evaluation could be obtained in our cohort to delineate which cognitive domains are more associated with abnormal TG in patients with PD. Moreover, longitudinal studies are needed to better understand the progression from normal TG to abnormal TG to progression to APPI in the majority of PD patients.

5. Conclusion

Tandem gait abnormality is common in PD patients and it preceded the development of APPI in our cohort. TG abnormality was statistically associated with subjective imbalance, history of falls, history of freezing of gait, S&E score less than 80, and MOCA score less than 24. Detecting TG abnormality in a patient with PD may predict fall risk. A follow up longitudinal study will help determine if TG is a predictor of impending progression from HY 2 to HY 3.

Author contributions

Jason Margolesky - conceptualized and designed the project and assessment protocol. Manuscript draft preparation.

Sagari Bette – patient assessments, provided critical review of manuscript.

Danielle S Shpiner – patient assessments, provided critical review of manuscript.

Elizabeth A Jordan – performed integral chart review, data collection and statistical analysis, provided critical review of manuscript.

Chuanhui Dong-performed statistical analysis, helped write method section of manuscript.

Tatjana Rundek – contributed to concept and design, provided critical review of manuscript.

Corneliu C Luca-contributed to concept and design, patient acquisition, provided critical review of manuscript.

Henry Moore - contributed to concept and design, patient acquisition, provided critical review of manuscript.

Carlos Singer-conceptualized and designed the project and assessment protocol, provided critical review and revision of manuscript.

Conflicts of interest in last 12 months

1. Jason Margolesky MD has no conflicts of interest to report.
2. Sagari Bette MD has no conflicts of interest to report.
3. Danielle S Shpiner MD has no conflicts of interest to report.
4. Elizabeth A Jordan has no conflicts of interest to report
5. Chuanhi Dong PhD has no conflicts of interest to report.
6. Tatjana Rundek MD PhD has no conflicts of interest to report.
7. Corneliu C Luca MD PhD has received educational grants from Medtronic and is a consultant for Abbott and Abbvie.
8. Henry Moore MD has no conflicts of interest to report.
9. Carlos Singer MD has received educational grants from Allergan and Medtronic, research grants from Adamas, Sunovion, Pfizer, Pharma2B and honoraria from Neurocrine

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