


Distal Upper Limb Tremor during Walking in Parkinson's Disease

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Abstract: Background: Distal upper limb tremor during walking (TW) is frequently observed in Parkinson's disease (PD) but its clinical features are unknown. Objective: To characterize the occurrence and the clinical features of TW in comparison to the other types of tremors in PD. Methods: Fifty-one PD patients with rest tremor were evaluated off- and on-treatment. Occurrence, body distribution, severity and latency of TW and of other tremor types were assessed. Results: TW was present in 78% of the PD patients examined. TW body distribution and severity were similar to those of rest and re-emergent tremor but different from the postural tremor presented by the same patients. TW latency, observed in 85% of patients, was on average 5.8 s. Dopaminergic treatment significantly improved TW, rest, and re-emergent tremor severity but left TW latency unaffected. Conclusions: TW is a frequent motor sign in PD and is likely a clinical variant of rest tremor.

Patients with Parkinson's disease (PD) may show various types of distal upper limb tremor.^{1–6} Typically, PD tremor is present at rest, and it disappears when the patient performs a voluntary movement (rest tremor).^{2,7–9} Tremor can also be observed while holding an upper limb posture. In this case tremor can be present after a variable delay (re-emergent tremor) or can appear immediately after reaching and holding a posture (postural tremor).^{10–12} Although both tremors appear during posture holding, re-emergent and postural tremor differ for the pathophysiological and clinical features.^{7,12,13}

In PD, distal upper limb tremor is often observed during walking (TW).¹⁴ In this case, TW appears during automatic upper limbs movements differing therefore from both rest condition and voluntary movement execution. To date, no studies have specifically investigated TW occurrence, clinical features and relationship with other tremors in patients with PD.

The present study aims to characterize the occurrence and clinical features of TW (amplitude, body distribution, latency,

response to dopaminergic treatment) compared to other types of tremors present in a cohort of 51 PD patients, tested off- and on-treatment.

Methods

Fifty-one PD patients were consecutively enrolled. PD patients were diagnosed according to international diagnostic criteria and had rest tremor.¹⁵ The disease stage was assessed using the Hoehn and Yahr scale (H&Y),¹⁶ whereas the severity of motor symptoms through the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS—UPDRS) part III.¹⁷ Patients were tested off-treatment as well as 60 minutes after taking their usual dopaminergic treatment (on-treatment evaluation). TW was defined as a tremor appearing immediately or after a variable time interval in the upper limbs of a patient who was asked to walk along a linear path with the

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arms relaxed for 120 seconds. In all patients, we evaluated the presence of rest, re-emergent and postural tremor. All patients underwent a standardized video recording and the presence and severity of various forms of tremor were evaluated off- and on-treatment. Other details on the assessment and study protocol are in the Supplementary materials.

Statistical Analysis

We used SPSS software (SPSS Inc., Chicago, IL, USA) version 25 for the statistical analysis. Descriptive analysis techniques were used for demographic and clinical data. The student's t-test, the Mann Whitney U test or the Wilcoxon signed-rank test were adopted in the univariate analysis as appropriate tools for comparing clinical characteristics of different types of tremors. (See Supplementary materials).

Results

Demographic and Clinical Features of PD Patients

The patients' demographic and clinical features are reported in Table S1. and in the Supplementary materials.

TW Occurrence, Body Distribution, Severity, Latency and Response to Dopaminergic Treatment

Occurrence: TW was present in 40/51 (78%) patients when evaluated off treatment and in 31/51 (61%) on treatment (See Table 1, Fig. 1).

Body distribution: when patients were evaluated off-treatment, TW was unilateral in 34 patients out of 40 (right side: 17 patients; left side: 17 patients) and bilateral in 6 of 40 patients. TW had the same body distribution (same side when unilateral or bilateral distribution for both tremors) of rest tremor in 95% (38/40) of cases, re-emergent tremor in 58% (23/40) of patients and postural tremor in 8% (3/40) of cases. In 40 out of 41 patients, TW was found in the most affected body side in terms of bradykinesia and rigidity. In the on-treatment evaluation, TW was unilateral in 27 patients and bilateral in 4 out of 31 patients (right side: 12 patients; left side: 15 patients). TW had the same body distribution of rest tremor in 94% (29/31) of cases, re-emergent tremor in 52% (16/31) of patients and postural tremor in 6% (2/31) of cases. In 39 out of 40 patients, TW was found in the most affected body side in terms of bradykinesia and rigidity (See Table 1).

Severity: TW mean severity was 2.4 ± 0.7 off-treatment and 1.9 ± 1.1 on-treatment. TW severity was higher than postural tremor ($U = 58.50$; $P < 0.001$) but similar to rest tremor ($P = 0.25$; $t = 1.134$, $df = 88$) and re-emergent tremor severity

TABLE 1 Occurrence and Clinical Features of Rest Tremor (REST), Re-Emergent Tremor (RET), Postural Tremor (PT) and Tremor During Walking (TW) off Treatment and on Treatment

	Off treatment evaluation					On treatment evaluation						
	Occurrence (%)	Mean amplitude	Mean latency (s)	Body distribution (%)			Occurrence (%)	Mean Amplitude	Mean latency (s)	Body distribution (%)		
				Right	Left	Bilateral				Right	Left	Bilateral
REST	100	2.25 ± 0.7	-	35.3	39.2	25.5	94	1.8 ± 0.8	-	38.8	42.9	18.3
RET	63	2.15 ± 0.8	6.2 ± 3.6	36.4	54.5	9.1	47	1.54 ± 1.1	8.6 ± 5.2	29.2	58.3	12.5
PT	21	1.4 ± 0.5	-	18.2	18.2	63.6	18	1.2 ± 0.4	-	25	12.5	62.5
TW	78	2.4 ± 0.7	5.8 ± 7.7	42.5	42.5	15	61	1.9 ± 1.1	5.5 ± 4.3	38.7	48.3	13

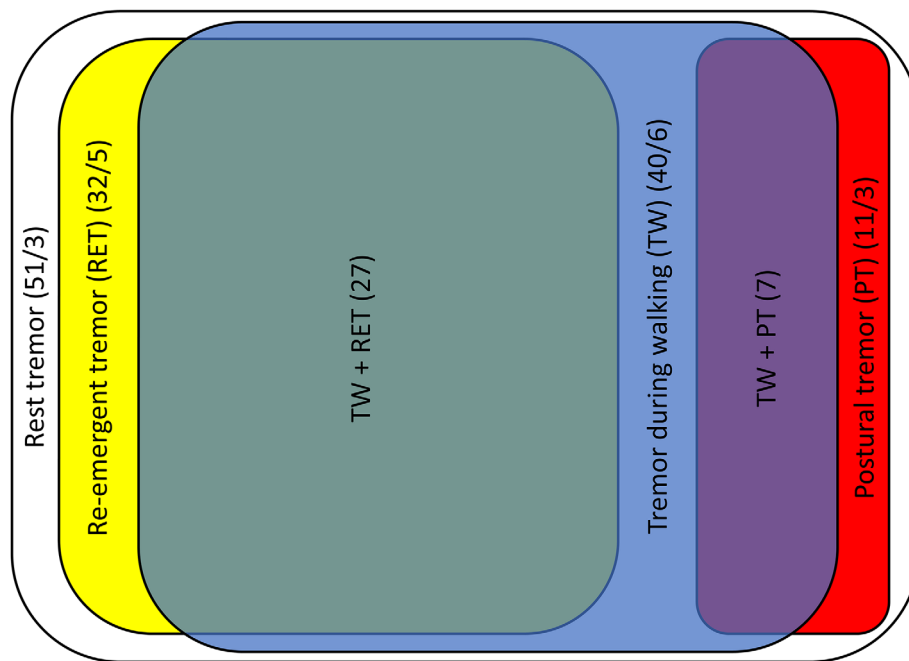


Figure 1. Occurrence of different types of tremors during off-treatment. Rest tremor was present in all patients. In the white square 51 indicates the total number of patients with rest tremor and 3 indicates the number of patients with isolated rest tremor. In the yellow square 32 indicates the total number of patients with re-emergent and 5 indicates the number of patients with only re-emergent. In the blue square, 40 indicates the total number of patients with tremor during walking and 6 indicates the number of patients with only tremor during walking. In red square, 11 indicates the total number of patients with postural tremor and 3 the number of patients with only postural tremor. In the green square, 27 indicates patients with both re-emergent tremor and tremor during walking. In the purple square, 7 indicates patients with both postural tremor and tremor during walking.

($P = 0.12$; $t = 1.589$, $df = 71$) when evaluated off-treatment. Similarly, when evaluated on-treatment, TW severity was similar to the severity of rest tremor ($P = 0.58$; $t = 0.547$; $df = 89$) and re-emergent tremor ($P = 0.15$; $t = 1.421$; $df = 71$) but higher than for postural tremor ($P = 0.003$; $t = 3.030$; $df = 49$). Dopaminergic treatment induced a significant TW ($P = 0.0005$; $t = 3.779$; $df = 39$), rest tremor ($P < 0.0001$; $t = 4.788$; $df = 49$) and re-emergent tremor improvement ($P = 0.0003$; $t = 4.070$; $df = 32$), whereas postural tremor amplitude remained unchanged after dopaminergic treatment ($W = -15$; $P = 0.0625$) (See Fig. S1.; Table 1).

Latency: TW started immediately after walking in 6 out of 40 and appeared after variable latency (ranging from 1 to 40 seconds) in 34/40 patients (85%). TW mean latency was 5.8 ± 7.7 seconds (range: 0–40 seconds) off-treatment and 5.5 ± 4.3 seconds (range: 0–42 seconds) on-treatment. Tremor started with latency in 85% of patients with TW and re-emergent tremor, and in 57% of patients with TW and postural tremor. In the off-treatment assessment, in patients with TW and re-emergent tremor the mean latency of re-emergent tremor (6.7 ± 3.66 seconds) was similar to TW latency (6.5 ± 5.91 seconds) ($P = 0.88$; $t = 0.146$; $df = 46$). Conversely, in the on-treatment evaluation on the same group of patients, the mean latency of TW (5.1 ± 3.33 seconds) was significantly lower than that of re-emergent tremor (9.1 ± 5.54 seconds) ($P < 0.0117$;

$t = 2.658$; $df = 36$). Based on the three clinical evaluations, we observed that the coefficient of variation was 9.2% for re-emergent tremor latency and 28.9% for tremor during walking latency. TW during walking and relative latency were consistently present in every measurement. Dopaminergic treatment did not significantly modify TW latency ($W = 96$; $P = 0.09$). Contrarily, re-emergent tremor latency was significantly prolonged by dopaminergic treatment ($W = 136$; $P = 0.001$) (See Fig. S2.).

Discussion

In the present study, TW was the most frequent tremor after rest tremor, being present in 78% of PD patients in the off-state. TW body distribution and severity were similar to those of rest and re-emergent tremor and different from those of postural tremor. TW started after a variable delay in 85% of patients. Dopaminergic treatment significantly improved TW as well as rest tremor and re-emergent tremor but left postural tremor unchanged.

We took several precautions to exclude methodological biases. To minimize selection bias, we consecutively recruited all PD patients who met the international diagnostic criteria and had rest tremor. In addition, video recordings of the different types of

tremors were separately evaluated by two different movement disorders specialists and satisfactory inter-rater reliability was observed for all tremor items. Finally, to exclude any confounding effects due to the patients' regular dopaminergic treatment, the clinical assessment in off-condition was performed at least 24 hours after treatment withdrawal.

In our study, TW represented the most frequent form of tremor observed in PD patients after rest tremor. TW has a similar occurrence to rest tremor, suggesting that TW is a form of rest tremor facilitated by walking, similar to what happens with emotional or cognitive stress.^{18–21} In line with this hypothesis, we observed that TW had a similar body distribution, severity and response to treatment of rest tremor as well as re-emergent tremor, that is now considered as a clinical variant of rest tremor.^{11,12,22,23} TW is unique for the motor context in which it occurs. Human walking, a complex behavior requiring the integration of multiple signals, is accompanied by automatically controlled movement processes, such as the adjustment of postural muscle or arm swings with the motion of the opposite leg.^{24,25} Then, unlike re-emergent and postural tremor that occur during a voluntary upper limb movement, TW occurs during automatic upper limb movements. Thus, TW may be a form of rest tremor occurring during automatic movements. In line with our hypothesis, it has been suggested that the simulation of walking in the sitting position facilitates the appearance of rest tremor in parkinsonian patients, possibly by activating common brain areas involved in gait control and tremor generation.²⁶

In recent years, clinical and neurophysiological studies have pointed out that rest and re-emergent tremor might represent different manifestations of a single underlying tremor mechanism^{11,12,22,23} and configure a clinical spectrum currently defined as “tremor of stability” ie a PD tremor appearing when a stable condition (resting state, posture maintaining) is reached.¹³ We now propose that TW may belong to this clinical continuum. In line with this, TW co-localization with the most bradykinetic side may be due to an abnormal “stability” from reduced arm swing during walking. This hypothesis is, however, speculative and needs to be validated by future neurophysiological studies, providing an objective measurement of TW and arm swing.

Similarly to re-emergent tremor, TW had a variable latency. As previously demonstrated, dopaminergic treatment increased re-emergent tremor latency²⁷ but left unchanged TW. The different responses to treatment may be explained by the tremor-related activity of non-dopaminergic brain regions,²⁸ such as the cerebellum, which plays a critical role in walking. However, further studies are needed to confirm this hypothesis.

We acknowledge some limitations. The major limitation of the present study is the lack of an objective measurement of TW and other PD tremors parameters. This limited the accuracy of the evaluation of clinical features. Future neurophysiological studies are needed to confirm the present findings. In addition, we tested every patient 60 minutes after L-Dopa intake and all patients showed clinical improvement, reaching their ON state. However, given we performed only one on-treatment clinical

assessment, we cannot fully ensure that they were at their best MDS-UPDRS score after 60 minutes.

To conclude, this is the first study specifically evaluating the clinical characteristics of TW in PD. Including TW examination may increase the sensitivity to identify and assess distal upper limb tremor in PD since rest tremor is subject to variability due to difficulties in relaxing, especially in the elders,²⁹ and emotional factors.^{17–19} Our clinical evaluation suggests that TW is present in most PD patients with rest tremor and shares common clinical features with rest and re-emergent tremor. If pathophysiological mechanisms underlying TW and those of rest and re-emergent tremor are similar remains an open question that will need to be clarified by future neurophysiological and neuroimaging studies.

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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.

M.C.: 1A, 1B, 1C; 2A, 2B, 2C; 3A, 3B

C.C.: 1A, 1B, 1C; 2A, 2B, 2C

G.L.: 1A; 2A, 2B; 3A

M.I.B.: 1B, 1C

A.F.: 1B, 1C

G.V.: 2C; 3B

A.C.: 1A; 2A, 2C; 3B

G.F.: 1A; 2A, 2C; 3B

A.B.: 1A; 2A, 2C; 3B

D.B.: 1A, 1B; 2A, 2B, 2C; 3A, 3B

Disclosures

Ethical Compliance Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local institutional review board (Sapienza University of Rome Ethics Committee, No. 5830). All patients were informed of the study purpose and written informed consent was obtained from all participants. 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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Supporting Information

Supporting information may be found in the online version of this article.

Supplementary Figure S1. Effect of dopaminergic treatment on clinical severity in different types of tremors. Tremor amplitude has been evaluated according the MDS-UPDRS item for resting, postural and action tremor (items 3–15, 3–16, 3–17). *Statistically significant differences ($P < 0.05$).

Supplementary Figure S2. Effect of dopaminergic treatment on the latency, as expressed in seconds, of tremor during walking (TW) and re-emergent tremor (RET). ns indicates no statistically significant difference. *Statistically significant differences ($P < 0.05$).

Supplementary Table S1. Demographic and clinical features of patients.

Supplementary Table S2. Interrater reliability.

Supplementary materials A more detailed description of methods, including clinical assessment and statistical analysis is provided. Additional results on demographic and clinical features of PD patients, interrater reliability and clinical characteristics of tremor during walking are also reported.