Action tremor in Parkinson's disease: frequency and relationship to motor and non-motor signs

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Background and purpose: Action tremor may occur in patients with Parkinson's disease and cause misdiagnosis with other movement disorders such as essential tremor and dystonia. Data on the frequency of action tremor in Parkinson's disease and on the relationships with other motor and non-motor signs are limited.

Methods: A cross-sectional study of 237 patients with Parkinson's disease staging 1–2 on the Hoehn−Yahr scale was conducted. Data on action tremor and other motor and non-motor signs were collected using the Unified Parkinson's Disease Rating Scale part III and the Non-Motor Symptoms Scale.

Results: Action tremor was found in 46% of patients and was associated with both severity of rest tremor (adjusted odds ratio 3.0, $P < 0.001$) and severity of rigidity (adjusted odds ratio 1.5, $P = 0.004$). No association was found between action tremor and severity of bradykinesia (adjusted odds ratio 0.97, $P = 0.4$) or axial symptoms (adjusted odds ratio 0.9, $P = 0.3$). Moreover, patients who had action tremor reported a significant lower mean number of non-motor symptoms than those who had not (2.1 ± 1.3 vs. 2.4 ± 1.3; $P = 0.04$).

Conclusions: Action tremor is a relatively frequent motor sign in patients with Parkinson's disease staging 1–2 on the Hoehn−Yahr scale. Action tremor correlates with rest tremor and rigidity and may be associated with a lower burden of non-motor symptoms. These findings suggest a contribution of non-dopaminergic mechanisms to action tremor pathophysiology.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by motor and non-motor manifestations. Bradykinesia, resting tremor (RT), rigidity and postural instability are cardinal motor signs whereas non-motor symptoms (NMS) belong to several domains including sleep disturbances, autonomic dysfunction, cognitive/neuropsychiatric symptoms, pain and olfactory disturbance.

In addition to classical RT, many PD patients also have action tremor (AT) occurring during sustained postures or voluntary movement [1,2]. Given that AT is the clinical hallmark of essential tremor and can also frequently occur in other movement disorders such as dystonia, the presence of AT may confound PD diagnosis, especially at the earlier stages. Since data on AT in PD are limited [2–8], the frequency of AT and its relationship to other motor and non-motor PD features were studied in a large series of patients staging 1–2 on the Hoehn−Yahr (H&Y) scale [9].

Methods

Patients were recruited amongst consecutive outpatients attending the movement disorder clinic of the

University of Bari during an 8-month period. PD was diagnosed according to UK PD Society Brain Bank criteria [10]. To avoid misdiagnosing a patient with essential/dystonic tremor as having PD, the presence of bradykinesia and levodopa response was monitored . Only patients staging 1–2 on the H&Y scale and reaching 24 or more on the Mini-Mental State Examination were enrolled. The study was approved by the ethics committee of the University of Bari and subjects gave informed consent for their participation.

Data collection and assessments

Demographic data (age, gender and years of schooling) and clinical information (age at disease onset, disease duration, severity of disease and medications) were collected by a medical interviewer. The levodopa-equivalent daily dose (LED) was calculated [11]. PD severity was assessed in the *on* state by the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) that allows separate evaluation of RT and AT [12]. UPDRS-III severity score of axial symptoms was the sum of speech, facial expression, arising from chair, posture, gait and postural stability scores. Non-motor symptoms were assessed by the validated Non-Motor Symptoms Scale that codes each NMS as 0 if absent, 1 if present [13]. NMSs were grouped in five domains including sleep disturbances (restless legs, periodic limb movements, rapid eye movement behaviour disorder, excessive daytime somnolence, vivid dreaming, non-rapid-eye-movement sleep-related movement disorders, insomnia), autonomic dysfunction (gastrointestinal tract, urinary tract, sexual function, cardiovascular), cognitive/neuropsychiatric dysfunction (apathy/attention/memory; hallucinations/delusions; depression/anxiety/anhedonia), pain and olfactory disturbance.

Statistical analysis

Statistical analysis was performed using the Stata 11.0 package (Stata Corporation, College Station, TX, USA). Data were expressed as mean ± SD unless otherwise indicated. Differences across groups were analysed by Mann–Whitney U test, chi-squared test and one-way analysis of variance (ANOVA), as appropriate. Univariable and multivariable logistic regression models were computed to compare motor and non-motor symptoms between PD patients who had AT and those who had not. Odds ratios, two-sided 95% confidence intervals and P values (likelihood ratio statistic) were calculated. Correlation analyses were performed by computing Spearman coefficient or regression coefficients (RCs) from linear regression models. Statistical significance was set at the 0.05 level.

Results

Demographic and clinical features of the study sample

Ninety-eight women and 139 men satisfied inclusion criteria during the study period and all participated in the study. Mean age at PD onset was 61.9 ± 10 years, and mean disease duration was 5.2 ± 3.8 years. Thirty-one patients staged 1 and 206 staged 2 on the H&Y scale. Eleven patients were drug-free on examination, whereas the others received antiparkinsonian medication including dopamine agonists alone (n = 38), levodopa alone (n = 42), catechol-O-methyltransferase/monoamine oxidase inhibitor alone (n = 14) and multiple dopaminergic drugs (n = 132). Mean LED was 476 ± 356 mg. The mean UPDRS-III score was 23.9 ± 10 (bradykinesia score 10.6 ± 5; rigidity score 4.4 ± 3; RT score 1.6 ± 1.9; AT score 0.7 ± 0.9; axial symptom score 5.3 ± 2.8). A significant correlation was found between bradykinesia and rigidity motor scores (ρ = 0.45, P < 0.001), whereas no correlation emerged between bradykinesia and RT scores (ρ = 0.11, P = 0.1) and between rigidity and RT scores (ρ = −0.04, P = 0.6). One affected NMS domain or more was reported by 216/237 patients; the average number of NMS domains per patient was 2.2 ± 1.3. Sleep disturbances were reported by 151/237 patients, autonomic dysfunctions were reported by 111/237 patients, cognitive/neuropsychiatric dysfunction was reported by 121/237 patients, and finally pain and olfactory disturbances were experienced by 77/237 and 73/237 patients respectively. There was a significant correlation between number of affected domains and UPDRS-III motor score (ρ = 0.15, P = 0.02).

Action tremor and parkinsonian motor signs

On clinical examination 108/237 (46%) patients had AT either alone (n = 18) or associated with RT (n = 90). The frequency of AT was similar in the patients staging 1 (15/31, 48%) or 2 (93/206, 45%) on the H&Y scale. AT was unilateral in 79/108 patients. No patient without AT on examination had evidence of AT on past history.

Patients who had AT (n = 108) and those who had not (n = 129) were similar for sex, age of disease onset, disease duration, UPDRS-III axial symptom score and bradykinesia score (Table 1). However, patients who did not have AT were preferentially on multiple drugs and showed a trend to a greater LED (Table 1). By contrast, the number of patients with

RT as well as UPDRS-III RT and rigidity scores was significantly greater in the AT group (Table 1). Multivariable logistic regression analysis (adjusted for sex, age at disease onset, disease duration and H&Y staging) including monotherapy/polytherapy, LED and UPDRS-III severity scores of axial symptom, rigidity, RT and bradykinesia yielded significant independent associations of AT with both RT and rigidity scores (Table 2). Neither significant association nor any trend was evident between AT and the other variables (Table 2). Confirming these findings, multivariable linear regression analysis showed significant correlation between severity of AT and severity of both RT (adjusted RC, 0.42; $P < 0.001$) and rigidity (adjusted RC, 0.09; $P = 0.03$); no correlation emerged between severity of AT and severity of bradykinesia (adjusted RC, -0.01; $P = 0.4$), severity of axial symptoms (adjusted RC, -0.01; $P = 0.8$) or LED (adjusted RC, -0.01; $P = 0.3$).

Action tremor and NMSs

Patients with AT had significantly lower mean number of NMSs than patients without AT (Table 3). Adjusting by sex, age at PD onset, disease duration and UPDRS-III motor score, multivariable logistic regression analysis yielded a non-significant trend towards a lower number of NMSs in the group with AT (odds ratio 0.83; 95% confidence interval 0.71–1.02; $P = 0.08$). The distribution of the various NMS domains did not differ between patients with and without AT (Table 3). There was a trend towards a significant reduction of NMSs in patients who had both AT and RT compared with patients who had one type of tremor alone and patients who did not

have tremor (2 ± 1.3 vs 2.4 ± 1.4 vs. 2.4 ± 1.3; one-way ANOVA, $F = 0.083$).

Discussion

In this sample of PD patients staging 1–2 on the H&Y scale, AT was present in 46% of cases and was independently associated with RT and rigidity. Patients with AT also manifested a tendency to a lower frequency of NMSs.

The frequency of AT reported by previous studies was greater than our estimate. Probably prior studies suffered from bias leading to overestimation of AT. In fact, studies assessing tremor by laboratory methods such as accelerometry or quantitative electromyography yielded an AT frequency ranging from 55% to 100% [2–7]. Otherwise, the clinical study by Louis *et al.* that observed AT in 93% of cases recruited PD patients in a single centre known for its expertise on tremor with the specific aim of assessing the relationship between AT and several demographical/clinical variables [8]. Therefore, the 46% frequency seen in our series seems to be a more likely estimate of AT manifesting in PD patients staging 1–2 on the H&Y scale.

Our multivariable analysis confirmed earlier observations indicating an association between AT and RT [6,8,14–16], which would indicate some common pathophysiological mechanisms between the two conditions [17–19]. It must be stressed, however, that AT in PD may have multifaceted phenomenology and, probably, pathophysiology [20]. Deuschl *et al.* distinguished three types of AT occurring in PD: type I, postural/kinetic tremor associated with classic parkinsonian RT with the same frequency; type II, rest and

Table 1 Demographical and clinical features of patients with Parkinson's disease with or without action tremor

	Patients with action tremor ($n = 108$)	Patients without action tremor ($n = 129$)	Odds ratio	95% confidence interval	P
Sex (women/men)	45/63	53/76	1.01	0.61–1.79	0.9
Age at disease onset (mean years ± SD)	61.4 ± 10.7	62.6 ± 9.7	0.99	0.96–1.01	0.4
Disease duration (mean years ± SD)	5.1 ± 3.7	5.2 ± 3.8	0.99	0.92–1.06	0.7
Treatment (monotherapy/ polytherapy/no drugs)	51/52/5	43/80/6	1.9[a]	1.1–3.1	0.02
Levodopa equivalent dose (mean ± SD)	435 ± 329	514 ± 374	0.999	0.99–1.00	0.1
Rest tremor (no. of patients)	90/108	57/129	6.39	3.46–11.8	<0.001
UPDRS-III motor score					
Axial symptoms (mean score ± SD)	5.1 ± 3	5.4 ± 2.6	0.96	0.88–1.05	0.4
Rest tremor (mean score ± SD)	2.4 ± 2.2	0.9 ± 1.2	2.82	2.08–3.81	<0.001
Rigidity (mean score ± SD)	5.1 ± 3	3.9 ± 3	1.43	1.17–1.75	0.001
Bradykinesia (mean score ± SD)	10.9 ± 5	10.4 ± 5.1	1.02	0.97–1.07	0.4

[a]The 11 patients who were not on dopaminergic treatment were excluded from analysis.

Table 2 Results of multivariable logistic regression analysis including number of patients on monotherapy, levodopa equivalent dose and UPDRS-III severity scores of axial symptoms, rest tremor, rigidity and bradykinesia

	Odds ratio	95% confidence interval	P
Dopaminergic monotherapy	1.33	0.60–2.92	0.5
Levodopa equivalent dose	0.99	0.99–1.01	0.6
Axial symptoms	0.92	0.79–1.07	0.3
Rest tremor	3.1	2.14–4.29	<0.001
Rigidity	1.2	1.09–1.42	0.001
Bradykinesia	0.97	0.89–1.05	0.5

Estimates were adjusted for sex, age of disease onset, disease duration and Hoehn–Yahr staging.

Table 3 Distribution of non-motor symptoms amongst patients suffering from Parkinson's disease with or without action tremor

	Patients with action tremor (n = 108)	Patients without action tremor (n = 129)	P
Number of non-motor symptoms (mean ± SD)	2.1 ± 1.3	2.4 ± 1.3	0.04
Number of patients with			
Sleep disturbances	66/108	85/129	0.3
Autonomic dysfunction	46/108	65/129	0.1
Pain	33/108	44/129	0.3
Olfactory disturbance	32/108	41/129	0.4
Cognitive/ neuropsychiatric symptoms	51/108	70/129	0.2

postural/kinetic tremor with different frequencies; and type III or pure postural/kinetic tremor without rest tremor [14]. The lack of information contained in the UPDRS-III on AT subtypes [12] did not allow us to check the relationship of RT with AT subtypes.

The relationship between AT and rigidity herein reported is a novel and intriguing finding that has little correspondence in the sparse literature on AT in PD. Two earlier studies did not find any correlation between AT and rigidity [8,21], whereas more recently Milanov reported that PD patients without postural tremor were less rigid [7]. Additional indirect evidence, including the neurophysiological similarities between AT and the cogwheel phenomenon usually associated with rigidity [2,6,22], the greater efficacy of DBS on tremor (including AT) and rigidity [23–25], and the combined presence of both AT and rigidity in other movement disorders such as dystonia and essential tremor [26–29], also supports a link between AT and rigidity.

Cardinal PD motor signs show different responsiveness to dopaminergic drugs [30,31] and also different relationships to the dopaminergic cell loss in the sub-

stantia nigra as evaluated by single photon emission computed tomography studies with [123I]FP-CIT [32–34]. Therefore, the lack of relationship between AT and bradykinesia (a cardinal PD motor sign that is strongly responsive to dopaminergic drugs and strongly relates to the dopaminergic cell loss in the substantia nigra) [32–34] and the relationship between AT and RT/rigidity (motor signs that are less or not related to the dopaminergic cell loss in the substantia nigra) [32–34] support a contribution of non-dopaminergic mechanisms to AT. Although the response of AT to dopaminergic drugs was not formally assessed, the lack of significant relationship on multivariable analysis between AT and LED and AT and presence of multiple drugs is in favour of our hypothesis. Further supporting this view, an earlier observation reported that nearly half of the PD patients who had AT improved with alcohol and even more cases with propranolol [35].

The lower frequency of NMSs in patients with AT is in line with the results of several studies indicating a lower frequency of NMSs in tremor-dominant PD [36–38]. This finding has been correlated to the most favourable course and clinical outcome characterizing tremor-dominant PD [39]. Of note, prior studies did not distinguish between AT and RT whilst our findings raise the possibility that NMSs are less prominent in patients who have both AT and RT. A more powerful study is needed, however, to confirm this view.

This study has limitations. First, our clinical study was based on a case series from a tertiary referral centre and therefore a selection bias cannot be ruled out. However, patients' recruitment was based on rigorous diagnostic criteria that produced a clinical series resembling the demographic and clinical features of the general population of PD cases staging 1–2 on the H&Y scale. The significant correlation between bradykinesia and rigidity severity and the lack of correlation between bradykinesia and RT severity and between rigidity and RT severity observed in our patients were in agreement with the literature [8]. Secondly, excluding patients with dementia the relationship between AT and cognitive impairment could not be assessed. However, Louis et al. [8] did not find any relationship between AT and Mini-Mental State Examination. Thirdly, assessments were performed when patients were in the on state. This might have been responsible, at least in part, for the lack of correlation observed between AT and bradykinesia, a motor sign that is strongly responsive to dopaminergic drugs. However, adjusting by several potential confounding factors including LED did not change the estimate of the association between AT and bradykinesia. Fourthly, data about the presence and severity

of AT were from UPDRS-III, a scale that does not distinguish between postural and kinetic tremor and between re-emergent and non-re-emergent tremor [12]. Therefore, these variables could not be used for stratification. AT in the lower limb was also not assessed because UPDRS-III does not carry such information. Fifthly, the small number of patients staging 1 on the H&Y scale did not allow separate analysis of the relationship between AT and the other variables in the two H&Y groups. However, estimates from multivariable analysis were always adjusted for H&Y stage. Sixthly, the lack of association between AT and single NMS domains might merely reflect lack of statistical power. Owing to the cross-sectional approach, finally, the temporal relationship between AT and RT/rigidity could not be validly assessed.

Despite the foregoing limitations, the results of our study on patients staging 1–2 on the H&Y scale suggest that AT is a relatively frequent motor sign, correlates with RT and rigidity, and is associated with a low frequency of NMSs. These findings are consistent with a contribution of non- dopaminergic mechanisms to AT.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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