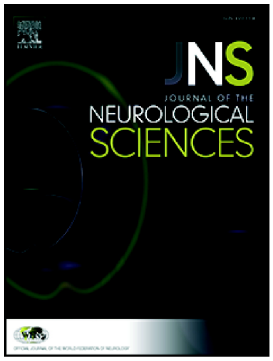

Rest tremor in Parkinson's disease: Body distribution and time of appearance

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Rest tremor in Parkinson's disease: body distribution and time of appearance

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Abstract

Objective. To assess body distribution and timing of appearance of rest tremor in Parkinson's disease.

Methods. Information was obtained by a computerized database containing historical information collected at the first visit and data collected during the subsequent follow-up visits. Information on rest tremor developed during the follow-up could be therefore obtained by our own observation in a proportion of patients.

Results. Among 289 patients, rest tremor was reported at disease onset in 65.4% of cases and detected at last follow-up examination in 74.4% of patients. Analysis of patients who did not report rest tremor at disease onset indicated that 26% of such patients (9% in the overall population) manifested rest tremor over the disease course. Rest tremor spread to new sites in 39% of patients who manifested rest tremor at disease onset. Regardless of tremor presentation at disease onset or during the follow–up, upper limb was the most frequent tremor localization. Over the follow-up, rest tremor developed faster in the upper limb than in other body sites. The risk of developing rest tremor during the follow-up was not affected by sex, side of motor symptom onset and site of tremor presentation. However, age of disease onset > 63 years was associated with an increased risk of rest tremor spread.

Conclusions. This study provides new information about body distribution and timing of rest tremor appearance during the course of early stages of Parkinson's disease that may help clinicians in patients' counselling.

1. Introduction

Tremor in a body part that is completely supported against gravity (rest tremor, RT) is among the core diagnostic features of Parkinson's disease (PD).[1,2] RT is thought to be more prevalent in the upper limb (UL) where it can coexist with action tremor (AT).[3, 4].

Information on the distribution of RT developed in various parts of the body at PD onset and during the disease course is limited. We identified only four studies investigating body distribution of RT at PD onset. Three of such studies detected RT in the UL in 42% to 65% of cases and in the lower limb (LL) in 3.7% to 24% of cases.[5-7]; one additional study detected RT in the jaw/lips (JL) in < 2% of cases.[8] A further study assessing the distribution of RT in 50 PD patients after several years of follow-up confirmed the greater frequency of RT in the UL.[9]

To our knowledge, no study has systematically compared body distribution of RT at disease onset and at follow-up, or provided information about the timing of RT appearance over the disease course. In this study, we reviewed the medical records of a large parkinsonian population in order to better characterize the trajectory of tremor across the first years after PD diagnosis.

2. Methods

Study subjects were recruited among consecutive outpatients attending the movement disorder clinic of our department over a 14-month period. The diagnosis of PD was made according to UK Parkinson's Disease Society Brain Bank criteria,[1] and disease was staged according with the Hoehn &Yahr (HY) scale.[10] All patients underwent head imaging studies (magnetic resonance imaging or computed tomography) as part of their diagnostic work up, and patients with focal brain lesions involving the basal ganglia or the brainstem were excluded. Patients with atypical parkinsonism, patients with history of recent use of drugs known to induce parkinsonism or to induce/enhance tremor, and patients with MiniMental State Examination < 24 were also excluded.[11]

Demographic and clinical information was obtained by a computerized database containing historical information collected at the baseline visit and information collected at the subsequent follow-up visits. At the first visit, demographic information, age at first motor symptoms, and presence of RT at PD presentation were recorded. Whenever possible, patient's historical report obtained at the first visit was supported by an informed relative or records from other physicians,

but these supports were not always available. After the first visit, patients were seen every six months on average and data about presence and severity of motor signs (assessed by the UPDRS-III scale) were recorded. Information on the timing of RT developed during the follow-up could be therefore obtained by our own observation in a proportion of patients. RT was examined in the *off* state while patients were in two different positions, i. e. lying down and sitting relaxed in an armchair with their hands fully supported by the armrest and feet (without shoes) comfortably supported on the floor. The most severe UPDRS-III rating was recorded. AT was defined as a tremor that occurred when the body part was required to maintain a posture (postural tremor) or perform a movement (kinetic tremor). The levodopa-equivalent daily dose (LEDD) at the last visit was calculated as previously reported. [12] Study protocol was approved by the local ethics committee.

Data were expressed as percentage or mean ± SD, and statistical analysis was performed by Stata 11.0 package (Stata Corporation, College Station, TX, USA). We used a two-sample t-test to determine whether a difference existed between the means of continuous data from the two groups of patients with and without tremor. One-way ANOVA (with Duncan post-hoc test) was instead use to test for differences among the mean time interval between disease onset and appearance of RT in three populations of patients who manifested tremor in the UL, LL, and JL. Comparison of proportions from patients with and without tremor was performed by Fisher test (two-tailed) or $\chi 2$ test as appropriate. The influence of sex, age at PD onset, and side of motor symptoms presentation on the risk of spread of RT to a second body part during the examined disease course was assessed by Cox proportional hazard survival analysis. Cox analysis allowed us to simultaneously estimate more than one predictor of tremor spread (multivariable analysis) by computing hazard ratio (HR) and 95% confidence interval (CI). The relationship between age at PD onset and spread of RT to a second body part was also estimated by Kaplan-Meier survival curves that were compared by means of the log-rank test. In both survival techniques, the response variable of interest was the amount of time from PD onset until the occurrence of tremor spread. Patients in whom spread

never occurred were included in the survival function for the duration of the observation, and their data were censored beyond that time. For all statistical analyses, p values < 0.05 were considered to be significant.

3. Results

Study population included 289 patients with idiopathic PD. There were 173 men and 116 women aged 67.5 ± 9.2 (range, 44-84) years. Age at PD onset was 62.5 ± 9.5 (range, 38-83) years. Patients were followed-up for 4.94 ± 3.92 years. At the last follow-up visit, most patients (n. 248) staged < 3 on the HY scale (mean ± SD, 1.8 ± 0.3) and scored 23.7 + 9.6 (range, 5 – 56) on the UPDRS-III scale. Two hundred and sixty-two patients were treated with levodopa, dopamine-agonists, or MAO/COMT inhibitors, alone or in combination [LEDD was 483.4 ± 344.3 mgs (range, 100-1770)], whereas 27 patients were drug-naïve. No patient had been treated with deep brain stimulation.

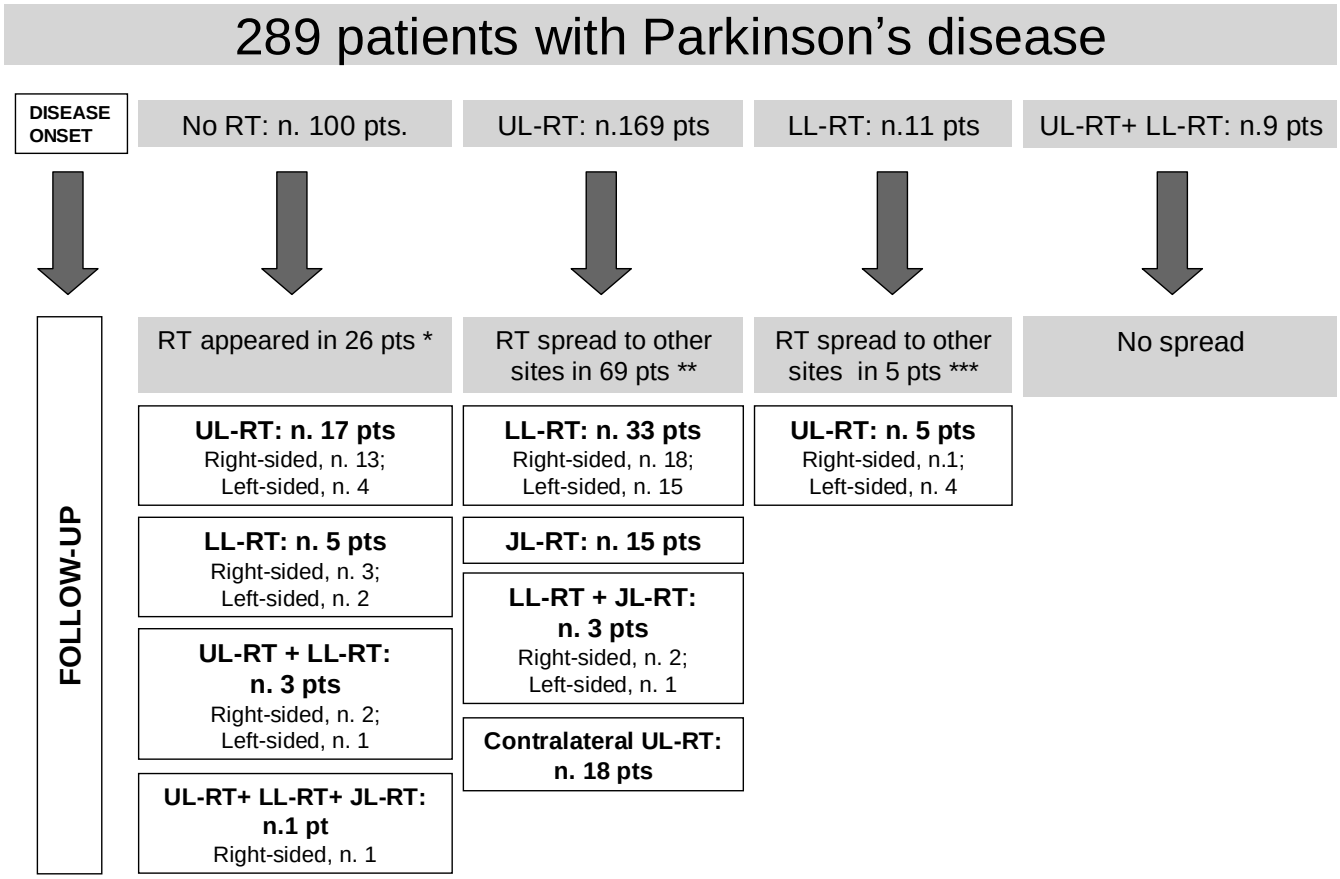
3.1 Rest tremor at disease onset

At PD onset, motor symptoms were right-sided in 168 patients, left-sided in 121 patients. One hundred out of 289 patients (35%) did not report tremor at disease onset whereas 189/289 patients (65%) reported unilateral RT (right-sided in 105 patients, left-sided in 84 patients). RT was localized in the UL (UL-RT) in 169/189 patients (89.4%), in the LL (LL-RT) in 11/189 patients, and in both UL and LL in 9/189 patients, whereas no patient manifested RT in the JL (JL-RT) (Figure1). Patients with and without RT at PD onset did not differ for sex (114 men and 75 women vs. 59 men and 41 women, p = 0.82), age of PD onset (62.9 ± 9.6 vs. 61.6 ± 9.2, p = 0.13), and side of first symptoms (right-sided, 105/189 vs. 63/100, p = 0.24).

3.2 Rest tremor developed during the follow up

Among the 100 patients who did not report tremor on PD onset, 26 (13 men and 13 women aged 63.2 ± 6.2 years at PD onset) developed RT during the follow-up (Figure. 1). This corresponded to 9% (26/289) of the whole population. In the group of 26 patients, RT appeared in the more affected side and more frequently affected UL than LL or JL (21/26 vs. 9/26 vs. 1/26 patients; chi-square test, $p<0.001$). The time interval between PD onset and appearance of RT in the 26 patients was shorter than the overall follow-up in the 74 patients who did not manifest RT [1.8 ± 1.9 (range, 0.5-4) vs. 5.4 ± 4.5 (range, 1-12) years, $p<0.001$). Similar findings were obtained when we analysed 10/26 patients in whom tremor was assessed by our own observation [2 ± 2.1 (range, 1-4) vs. 5.4 ± 4.5 (range, 1-12) years, $p=0.01$]. In the group of 100 patients, multivariable Cox analysis showed that the risk of developing RT during the follow-up was not affected by sex (adjusted HR, 1.58; 95% CI, 0.65 – 3.82; $p = 0.31$), age at PD onset (adjusted HR, 1.03; 95% CI, 0.98 – 1.08; $p = 0.19$), and side of motor symptom onset (adjusted HR, 1.56; 95% CI, 0.59 – 3.61; $p = 0.41$).

Fig. 1 Body distribution of rest tremor in the study population at disease onset and on follow-up

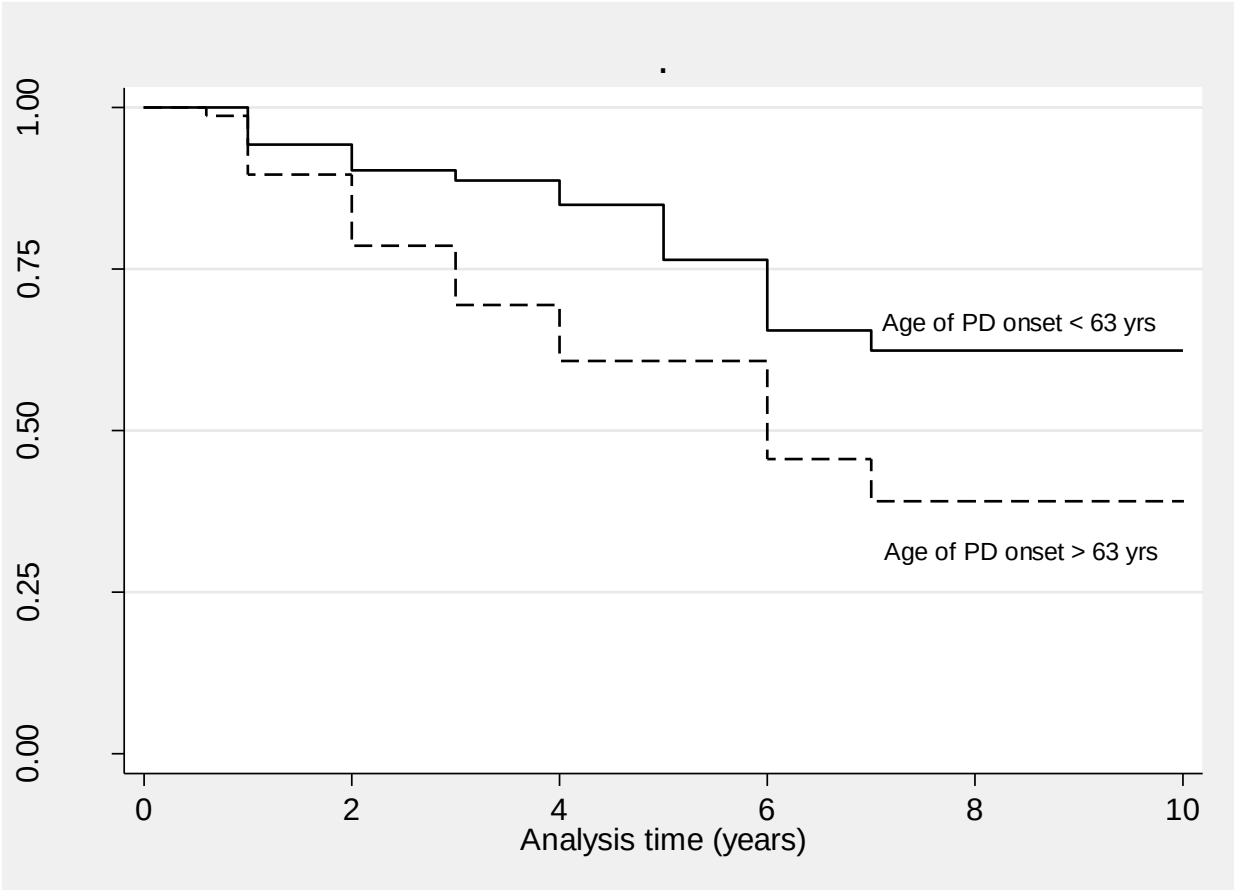


RT = rest tremor; UL-RT = upper limb rest tremor; LL-RT = lower limb rest tremor; JL-RT = jaw/lip rest tremor
tremor was assessed by our own observation in * 10 patients, ** 30 patients, and *** 3 patients

Among the 189 patients who reported RT at PD onset, 74/189 (46 men and 28 women aged 64.6 ± 8.6 years at PD onset, 39%) manifested spread of RT to additional sites during the follow-up. (Figure 1). Spread of RT occurred on the same side of disease onset (n. 41 patients), or followed diffusion of PD to the other side (n. 18 patients); in 15 patients tremor spread to the face. The time interval between disease onset and spread of RT was shorter than the overall follow-up of the 115 patients who did not manifest RT spread [3.1 ± 2 (range, 0.5-7) vs. 4.9 ± 4 (range, 1-12) years, $p<0.001$]. Similar findings were obtained when we considered only the 33/74 patients in whom tremor was assessed by our own observation [2.9 ± 2.3 (range 0.5-7) vs. 4.9 ± 4 (range, 1-12) years, $p=0.007$). Multivariable Cox analysis showed that the risk of RT spread to a second body part was not affected by sex, side of motor symptom onset and site of tremor presentation (upper limb vs.

lower limb); by contrast, age of PD onset was associated with an increased risk of RT spread (Table 1). Stratifying age of PD onset by the median value (63 years) yielded an increased risk of RT spread (adjusted HR, 2.05; 95% CI, 1.25 – 3.67; p = 0.01) in the patients aged 63 years or more at PD onset (Figure 2).

Figure 2. Kaplan–Meier survival analysis of spread of rest tremor to a second body part: Study time was represented by the time elapsed between onset of parkinsonian motor symptoms and spread of tremor. Patients in whom spread never occurred were included in the survival function for the duration of the observation. The number of at risk patients was 189 at time zero, 60 at 5 yr, and 16 at 10 yr.



Overall, RT manifested during the follow-up in 26 + 74 = 100/289 patients (35%) (Figure 1). When we analysed the time interval between disease onset and appearance of RT in the 100 patients, we observed that UL-RT (n. 44 patients) developed faster than LL-RT (n. 45 patients) and JL-RT (n. 19 patients): 1.2 ± 1.1 (range, 0.5-4) vs. 3.1 ± 1.9 (range, 2-7) vs. 3.5 ± 2.3 (range, 1-7) years (One way ANOVA: $F = 11.9$, $p<0.001$; Duncan's post hoc test: UL-RT group vs. all other groups, $p<0.05$). Similar findings were obtained when we limited analysis to the 43/100 patients (18 with UL-RT, 21 with LL-RT and 10 with JL-RT) who had RT appearance assessed by our own observation [1.3 ± 1.2 (range, 1-3) vs. 3.4 ± 2.6 (range, 2-6) vs. 3.7 ± 1.9 (range, 2-7) years. One way ANOVA: $F = 4.2$, $p< 0.05$; Duncan's test: UL-RT group vs. all other groups, $p<0.05$].

Table 1. Results of multivariable Cox regression analysis assessing the risk of spread of rest tremor to a second body part by sex, age of onset of parkinsonian motor symptoms, side of motor symptom onset, and site of tremor presentation (upper limb vs. lower limb/face).

Variable	Hazard ratio	95% confidence interval	P
Women sex	0.72	0.39 – 1.34	0.31
Age of PD onset (years, continuous variable)	1.04	1.002 – 1.07	0.038
Right-sided onset of motor symptoms	1.39	0.78 – 2.47	0.26
Tremor presentation in the upper limb	1.07	0.41 – 2.76	0.88

3.3 Rest tremor and other features at the last follow-up visit

At the last follow-up visit, 215/289 patients (74.4%) manifested RT in the UL (n. 204/215, 94.9%), LL (n. 65/215, 30.2%) and JL (n. 19/215, 8.8%). Patients who did not manifest RT on examination (n. 74) had never had RT in the past. AT in the UL was found in 126/289 (43.4 %) patients (n. 106 patients with both RT and AT and n. 20 with AT alone). Although we lacked information about the number of patients who had AT at PD onset, we observed AT in 94/178 patients (53%) who reported UL-RT at disease onset and in 12/26 patients (46%) who developed RT during the follow-up ($p = 0.53$).

Patients with and without RT at the last follow-up visit had similar UPDRS-III motor score (23.8 ± 9.9 vs. 23.3 ± 8.8, $p = 0.35$). Excluding tremor items from UPDRS-III calculation, however, yielded a lower UPDRS-III motor score in patients with RT (21.2 ± 9.2 vs. 23.3 ± 8.8, $p = 0.044$). Duration of disease at the last follow-up visit (4.9 ± 3.8 vs. 5.1 ± 4.2 years, $p = 0.35$) and LEDD (420 ± 358 vs 403 ± 304 mgs, $p=0.36$) were similar in the two groups.

When we analysed UPDRS-III outcome in the 189 patients who presented with RT at PD onset we observed that patients with RT spread reached a greater UPDRS-III motor score at the last follow-up visit than patients who did not spread (26.2 ± 10.4 vs. 21.2 ± 8.9, $p = 0.0005$). However, the difference between groups lacked significance after excluding tremor items from UPDRS-III calculation (21.2 ± 8.4 vs. 19.6 ± 7.9, $p = 0.1$). Duration of disease at the last examination (4.9 ± 4.2 vs. 4.9 ± 3.7 years, $p = 1$) and LEDD (413 ± 355 vs. 420 ± 373 mgs, $p = 0.45$) were similar in the two groups.

4. Discussion

In this sample, RT was reported by 65.4% patients at disease onset and detected in 74.4% of patients on the last follow-up examination. Analysis of patients who did not report RT at disease onset indicated that 26% of such patients (9% in the overall population) manifested RT over the disease course. We also observed that RT spread to new sites in 39% of patients who manifested RT at disease onset. Regardless of RT presentation at disease onset or during the follow–up, UL was the most frequent tremor localization, followed by LL and JL. Over the follow-up, RT developed faster in the UL than in other body sites. The risk of developing RT during the follow-up was not affected by sex, side of motor symptom onset and site of tremor presentation. However, age of PD onset > 63 years was associated with an increased risk of RT spread.

The prevalence figures of RT we observed at disease onset and at the last examination are close to those reported by a few published studies. [3, 6-8, 10, 13-15] However, the 9% frequency of new cases of RT appearing during the follow-up and the 39% frequency of RT spread to new sites are novel findings that can not be compared with any previous data. The validity of these estimates is strengthened by the observation that the duration of follow-up in patients who did not manifest RT was longer than the time interval between PD onset and appearance of RT.

The greater occurrence of RT in the UL confirms the findings of previous studies, even though the frequency estimate of RT in each body part at disease onset and at the last follow-up visit was partly at variance with data from earlier studies (Table 2). Methodological differences probably explain discrepancies across studies. For instance, the longer disease duration characterizing the studies by Liu [7] and Uitti [8], might have affected the accuracy of tremor self-report. The greater LL-RT estimates provided by the studies by Gowers [5] and Patrick and Levy [6] could be related to the observation that these studies were performed before the advent of neuroimaging. It is therefore possible that some patients have been affected by atypical or secondary parkinsonisms, conditions that are frequently characterized by tremor in the lower limb as initial presenting symptom.[16] Finally, the only one study providing data on the body

distribution of RT after several years follow-up was characterized by a small size of the sample, which may have reduced the accuracy of the observation.[9]

Table 2. Frequency of occurrence and body distribution of rest tremor in clinical series of patients with sporadic Parkinson's disease. Data is expressed as ratio of number of tremulous patients/total number of patients. Percentages are in parenthesis.

	DISEASE ONSET			FOLLOW-UP		
First author, year	Upper limb rest tremor	Lower limb rest tremor	Jaw/lip rest tremor	Upper limb rest tremor	Lower limb rest tremor	Jaw/lip rest tremor
Gowers, 1888	41/63 (65.1%)	9/63 (14.3%)	0	-	-	-
Patrick and Levy, 1922	88/146 (60.3%)	15/146 (10.3%)	0	-	-	-
Uitti, 2005	522/1244 (42%)	46/1244 (3.7%)	21/1244 (1.7%)	-	-	-
Sternberg, 2013	-	-	-	20/50 (40%)	6/50 (12%)	7/50 (14%)
Liu, 2014	80/180 (44.4%)	43/180 (23.9%)	-	-	-	-
Present study, 2016	178/289 (61.6%)	20/289 (6.9%)	0	204/289 (70.6%)	65/289 (22.5%)	19/289 (6.6%)

The predominance and faster development of RT in the UL would suggest that this body part is more prone to tremor, or that LL and JL are more resistant to shaking. Owing to a wider range of movements, regulatory motor mechanisms are more complex in the UL and might therefore be more easily disrupted at a level provoking tremor in the hand than in other sites.[17] These considerations also apply to non parkinsonian tremors like essential tremor and dystonic tremor. [18, 19] The greater vulnerability of UL to tremor in PD and in other tremor conditions [18,19] raises the possibility of common pathophysiological mechanisms shared by apparently different forms of tremor. This is supported by recent evidence suggesting an involvement of

cerebellum in parkinsonian, essential and dystonic tremor, [20-22] and by the observed improvement of different types of tremor by surgical procedures targeting the same area.[23, 24]

We could not find any influence of sex and side of motor symptoms onset on the risk of developing RT during the follow-up. However, we observed and increased risk of RT spread to further sites in patients aged 63 years of more at PD onset, a novel observation that that can not be compared with any previous data.

Information from UPDRS-III motor score at the last follow-up visit is an agreement with a large body of data indicating a lower severity of PD in tremor dominant patients. However, we could not find any difference in the severity of non tremor symptoms between patients who manifested spread of RT and those who did not.

This study may have limitations. Recall bias could have been a concern in patients who self-reported RT development. To limit this bias, we recruited patients with early PD and MMSE $\geq$ 24. These criteria were probably responsible for the greater frequency of patients staging < 3 on the HY stage and for the relatively short mean duration of follow-up. Therefore, information from our sample mainly refers to the early course of PD. Supporting the validity of self-reported data about the timing of tremor appearance during the follow-up, findings did not consistently change when we separately analyzed 43% of patients who had tremor appearance assessed by our own observation. Owing to the retrospective assessment of disease onset, we did not evaluate the possible relationships between severity of parkinsonian symptoms at baseline and spread of tremor. In this study, we could not evaluate AT at disease onset because our historical interview focused only on the appearance of RT. The close relationship between RT and AT on examination confirmed an earlier study from our group indicating that AT usually affects the UL and coexists with RT in a proportion of cases.[4] Most patients were on dopaminergic medication, but the well known observation that no drug can consistently relieve RT [25], and the similar LEDD observed in the group with and without RT made underestimation of RT occurrence by drug regimen unlikely.

In conclusion, this study provides new and probably valid information about body

distribution and timing of RT development during the early course of PD. Our estimates may help clinicians to better counsel PD patients with regard to RT, one of the core parkinsonian motor signs that often can not be consistently relieved by antiparkinsonian therapy. [25]

Conflict of Interest and Sources of Funding Statement: Nothing to report

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Highlights

We studied body distribution and time of appearance of rest tremor in a large parkinsonian population

Rest tremor was reported by 65.4% of patients at disease onset

Rest tremor was described in 74.4% of patients on last follow-up examination

Rest tremor involved the upper limb more frequently than other body sites

During the follow-up, rest tremor developed faster in the upper limb than in other body sites