Parkinsonism and Related Disorders xxx (2016) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Re-emergent tremor in Parkinson's disease

Daniele Belvisi [a], Antonella Conte [a, b], Matteo Bologna [a, b], Maria Carmela Bloise [b], Antonio Suppa [a, b], Alessandra Formica [b], Matteo Costanzo [b], Pierluigi Cardone [b], Giovanni Fabbrini [a, b], Alfredo Berardelli [a, b, *]

[a] Neuromed Institute IRCCS, Via Atinense 18, 86077, Pozzilli (IS), Italy
[b] Department of Neurology and Psychiatry, "Sapienza" University of Rome, Viale dell'Università 30, 00185 Rome, Italy

ARTICLE INFO

Article history:
Received 13 September 2016
Received in revised form
4 November 2016
Accepted 15 December 2016

Keywords:
Re-emergent tremor
Rest tremor
Action tremor
Parkinson's disease
Subtype

ABSTRACT

Introduction: Re-emergent tremor (RET) is a postural tremor that appears after a variable delay in patients with Parkinson's disease (PD). The aim of the present study was to evaluate the occurrence and the clinical characteristics of RET in a population of patients with PD.
Methods: We consecutively assessed 210 patients with PD. We collected the patients' demographic and clinical data. RET was clinically characterized in terms of latency, severity and body side affected. We also investigated a possible relationship with motor and non-motor symptoms and differences in the clinical features in patients with and without RET.
Results: RET was present in 42/210 patients. The mean latency of RET was 9.20 ± 6.8 seconds. Mean severity was 2.4 ± 1.9. RET was unilateral in 21 patients. Patients with RET had less severe speech, posture and gait disorders and upper limb and global bradykinesia than patients without RET. Similar findings were observed when we compared patients with RET with patients with tremor at rest associated with action tremor, patients with isolated action tremor and patients with no tremor. By contrast, patients with RET tremor did not clinically differ from those with isolated tremor at rest.
Conclusion: Our results suggest that patients with RET and patients with isolated tremor at rest represent the same clinical subtype, whereas patients with action tremor (whether isolated or associated with tremor at rest) might belong to a distinct subtype that is clinically worse. Patients with RET represents a benign subtype of PD, even within the tremor-dominant phenotype.

1. Introduction

Patients with Parkinson's disease (PD) may display different types of tremor. Tremor at rest (RT) is common in PD [1,2], though postural and kinetic tremors may also be present [3–5]. Jankovic et al. described 12 PD patients with RT that showed a postural tremor that appeared after a variable delay when the upper limbs had been held outstretched [6]. The authors defined this tremor as "re-emergent tremor" (RET) and suggested that RET might be a possible clinical variant of RT [6]. This hypothesis was based on the observation that the two tremors share similar frequency characteristics [6,7] and a similar asynchronous muscle activation pattern [8].

Investigating a population of 197 PD, Louis et al. found 67 patients with RET (32%) but did not investigate the clinical features of this type of tremor [4]. As the clinical features of RET have never been exhaustively investigated, it is still unclear whether PD patients with RET differ from PD patients with other types of tremor and thus represent a distinct clinical subtype of PD.

The aim of the present study was to assess the occurrence of RET and to describe the characteristics of RET in a sample of 210 consecutive PD patients evaluated on their usual treatment regimen. We also sought a possible relationship between RET and other motor and non-motor symptoms of PD. Lastly, to investigate whether the presence of RET is indicative of a particular subtype of PD, we compared the clinical features of PD patients with RET with those of patients with other types of tremor and of patients

* Corresponding author. Department of Neurology and Psychiatry, and Neuromed Institute, Sapienza, University of Rome Viale dell'Università 30, 00185 Rome, Italy.
E-mail addresses: daniele.belvisi@uniroma1.it (D. Belvisi), antonella.conte@uniroma1.it (A. Conte), matteo.bologna@uniroma1.it (M. Bologna), bloise.mc@gmail.com (M.C. Bloise), antonio.suppa@uniroma1.it (A. Suppa), alessandraformica@yahoo.it (A. Formica), matteo_cos90@hotmail.it (M. Costanzo), pierluigicardone91@gmail.com (P. Cardone), giovanni.fabbrini@uniroma1.it (G. Fabbrini), alfredo.berardelli@uniroma1.it (A. Berardelli).

http://dx.doi.org/10.1016/j.parkreldis.2016.12.012
1353-8020/

without tremor.

2. Methods

2.1. Subjects

We consecutively assessed 210 patients with PD who were attending our Movement Disorder outpatient clinic, between January and June 2015. The diagnosis of PD was based on clinical criteria [9,10]. We collected the PD patients' demographic and clinical data, including age, age at onset, disease duration, duration of treatment with dopaminergic drugs, dosages of dopaminergic therapy, and presence of dyskinesia and motor fluctuations. The severity of the disease was assessed by means of the Hoehn and Yahr scale (H&Y) [11] and Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS - UPDRS) part III [12]. Non-motor symptoms were evaluated by means of the Non-Motor Symptoms assessment scale for PD (NMSS) [13]. The levodopa-equivalent daily dose (LEDD) was calculated.

In order to assess the presence of RT we asked patients to sit comfortably on a chair, with the upper limbs at rest for 60 seconds. To evaluate the presence of RET and postural tremor, we asked patients to extend both arms and to hold them outstretched for 90 seconds. Lastly, to assess the presence of kinetic tremor, we asked patients to perform the finger-to-nose and finger-to-finger tests (15 times for each side for each test).

RET was defined as a tremor that appeared in the outstretched upper limbs after at least 1 second while maintaining the posture [6]. In patients with RET, we carefully evaluated the latency (time interval between the arm extension and the onset of tremor, expressed in seconds), severity (0–4 according to the MDS-UPDRS) [12] and body side affected (unilateral or bilateral).

The clinical evaluation, including the H&Y and MDS-UPDRS scales and the assessment of the different types of tremor, was performed while patients were on their usual treatment regimen. After 3 months from the first clinical assessment, all the patients with PD underwent a re-evaluation performed by the same rater without checking previous data.

All the patients enrolled participated in the study. Each patient signed an informed consent form and the study was approved by the local ethics committee.

2.2. Statistical analysis

We performed a multivariate analysis to investigate which variable ("gender", "age", "age at onset", "disease duration" or "tremor type") best discriminated the clinical subtypes, stratified according to the characteristics of tremor. The demographic and clinical features were compared in patients with unilateral or bilateral RET by using a Mann-Whitney *U* Test. In patients with bilateral RET, we used a Mann-Whitney *U* test to compare the mean latency between patients with the right and the left affected body side. In patients with RET, we also evaluated possible correlations between RET severity and other demographic and clinical features by means of a Spearman rank correlation coefficient.

To ascertain whether patients with RET represent a distinct PD subtype, we compared the demographic and clinical features of patients with RET with those of patients without RET by using a Mann -Whitney *U* Test. In a subsequent analysis, we compared the demographic and clinical features of patients with different types of tremor and with no tremor by using a Kruskall Wallis test with the between group factor GROUP as main factor of analysis. The Mann-Whitney *U* test was performed for the post-hoc analysis.

A multiple logistic regression analysis with RET (1, present; 0, absent) as the outcome variable was performed to investigate the association with motor and non-motor symptoms and the possible confounding effect of relevant demographic and clinical variables. Odds ratios, two-sided 95% confidence intervals and P values (likelihood ratio statistic) were calculated. A subsequent stepwise analysis was performed.

In order to verify whether the classification of clinical subtypes was correct, we performed a Wilcoxon test to evaluate whether the patients' classification according to their tremor subtypes changed at a second assessment performed the 3-months later.

Holmes' correction was applied for multiple comparisons and correlations. P values < 0.05 were considered to indicate statistical significance.

We used SPSS software for the statistical analysis.

3. Results

3.1. Demographic and clinical features of PD patients

Eighty-two women and 128 men participated in the study. Their mean age was 70.4 ± 8.8 years, mean age at onset of parkinsonian symptoms was 62.3 ± 10.4 years and mean disease duration was 7.6 ± 5.2 years. The mean H&Y score was 1.9 ± 0.8 and mean MDS-UPDRS part III score was 24.3 ± 12.5. Six patients were drug-free. The remaining patients received antiparkinsonian medication, including levodopa alone (48), dopamine agonists alone (29), monoamine oxidase inhibitor alone (11) and a combination of drugs (116). Dyskinesias were present in 42 patients. Motor fluctuations were present in 101 patients.

3.2. Clinical subtypes according to the characteristics of tremor

The clinical evaluation disclosed that RET was present in 42 patients (20%), isolated RT in 18 patients (8%), RT associated with action tremor (AT) (postural and/or kinetic) in 82 patients (40%), isolated AT in 6 patients (2%), while the remaining 62 patients had no tremor (30%). The demographic and clinical data of the five subtypes of patients are reported in Table 1.

3.3. Multivariate analysis

The multivariate analysis showed that, among the several clinical and demographic features, "type of tremor" best discriminated the PD sample in the five subgroups ($p < 0.001$).

3.4. Characteristics of RET

The mean latency of RET was 9.2 ± 6.8 seconds (range: 1–35 seconds), and the mean severity 2.4 ± 1.9 (range1–4). All patients with RET were right-handed. RET was unilateral in 21 (right side: 13 patients; left side: 8 patients) and bilateral in 21 of the 42 patients. Fifteen patients with unilateral RET also had unilateral RT and 6 had bilateral RT. Both types of tremor (RT and RET) were present on the same side in the majority of cases (14 of 15 cases). In the 21 patients with bilateral RET, RT was bilateral in 17 patients and unilateral in 4 patients. In patients with bilateral RET, we found a similar mean latency between the right and the left sides (mean latency: right side: 9.0 ± 6.6 seconds; left side: 9.4 ± 7.1, $p > 0.05$).

When we compared the demographic and clinical features of patients with unilateral RET with those of patients with bilateral RET, we found no differences of the demographic or clinical variables considered (all ps > 0.05).

In patients with RET, we found a significant positive correlation between RET severity and ipsilateral RT severity (right side: $r = 0.65$; $p < 0.0001$; left side: $r = 0.46$; $p < 0.002$). We did not

Please cite this article in press as: D. Belvisi, et al., Re-emergent tremor in Parkinson's disease, Parkinsonism and Related Disorders (2016), http://dx.doi.org/10.1016/j.parkreldis.2016.12.012