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Latency of re-emergent tremor in Parkinson's disease is influenced by levodopa

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ABSTRACT

Introduction: Re-emergent tremor (RET) is a common form of postural tremor observed in Parkinson's disease (PD) patients. Recent studies have shown that administration of levodopa decreases RET amplitude. However, drug effects on tremor pause duration are less clear.

Methods: We performed a prospective observational study in PD patients with RET, subjected to acute levodopa challenge. Tremor activity was measured during OFF and ON states both clinically, as well as by using accelerometers taped to the back of both hands. Correlation between RET amplitude and pause duration, as well with MDS-UPDRS scores were investigated. The slope of gradual increase of postural tremor after the pause was also measured in the OFF and ON states.

Results: Significant inverse correlation between tremor amplitude and RET pause duration was observed in OFF ($rs = -0.474$, $p = 0.030$) and ON ($rs = -0.569$, $p = 0.006$) states. Levodopa reduced tremor amplitude (26%, $p = 0.004$) dampening slope gradient (22%, $p = 0.029$). Tremor pause duration also showed inverse correlation with postural tremor amplitude measured by MDS-UPDRS in OFF ($rs = -0.311$, $p = 0.048$) and ON ($rs = -0.503$, $p = 0.020$) states, as well as with total MDS-UPDRS Part III score ($rs = -0.295$, $p = 0.009$). Finally, accelerometric analysis proved to be more sensitive than visual inspection for detecting tremor pauses.

Conclusion: Our results suggest RET pause duration is amplitude related, since levodopa-induced amplitude decrease led to pause prolongation, associated with decreased tremor intensity and slope gradient dampening.

1. Introduction

Parkinsonian rest tremor is one of the cardinal signs of Parkinson's disease (PD) [1]. However, many patients may also present postural or kinetic tremor [2] of variable magnitude [3].

One typical aspect of parkinsonian tremor is that it ceases or diminishes considerably with muscular activation, while executing specific movements or maintaining a fixed posture [4–6]. About two thirds of patients with postural tremor also present what has been defined as re-emergent tremor (RET) [3,7], an extension of rest tremor, inhibited by movement and reappearing after a brief pause, without apparent change in frequency [8,9]. RET has recently attracted interest, as it is considered characteristic of parkinsonian tremor, distinguishing it from other forms [3,10].

Rest tremor and RET are commonly considered to be two manifestations of a continuum, as both share the same central generator [8]. Two recent articles have shown that levodopa lowers the amplitude of this form of postural tremor [11,12]. However, effects of the medication on pause duration have not been clearly established. The pause duration is a valuable clinical sign helping to differentiate different types of tremor. A study by Papengut et al. [10] has concluded that the evaluation of rest tremor suppression during movement initiation is a reliable tool to differentiate parkinsonian rest tremor from rest tremor in essential tremor. Jankovic et al. [3] initially described re-emergent tremor in 1999, as a feature that can differentiate parkinsonian tremor from postural tremor of essential tremor.

We hypothesize that RET pause duration depends on tremor amplitude, and therefore also on the sensitivity of method used to detect it. For that reason, tremor dampening with levodopa should be associated with pause prolongation. In this study we evaluated the summation of tremor contributions in the whole upper extremity and compared clinical impression and accelerometric measurement of the pause.

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2. Methods

We performed a prospective observational study evaluating the effects of levodopa on re-emergent tremor pause, through modification of its amplitude. Evaluations were conducted by accelerometric analysis of hand movements during a levodopa challenge test. The IRB approved the study which was conducted following Good Clinical Practice (GCP) standards and in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

2.1. Subjects

Consecutive adult patients were prospectively recruited from a tertiary Movement Disorders Clinic. All candidates selected met MDS clinical diagnostic criteria for Parkinson's disease [13], had been diagnosed with PD by a Movement Disorders specialist, and presented clinically evident rest and RET on physical examination. Patients had to be 18 years of age or older, Hoehn and Yahr stages I-III and have given informed consent. Subjects with other known causes of tremor, recent exposure to tremorgenic drugs, or coexistence of PD and essential tremor were excluded from the analysis. Patients with anatomic or orthopedic upper limb disorders, or those unable able to discontinue symptomatic medication, were also excluded.

2.2. Recordings during visits

Prior to acute levodopa challenge [14] test, patients were instructed to discontinue antiparkinsonian medication for at least 12 h in the case of levodopa and 24 h for dopamine agonists. Motor features were first assessed during the OFF state (baseline) and then every 20 min after receiving 250/25 mg of levodopa/carbidopa, until lowest motor score was registered using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III.

Baseline rest tremor activity was registered with patients comfortably seated, hands resting on lap in semiprone position. Recordings continued while patients were asked to stretch out their arms at a 90° angle to the trunk, palms facing downwards, maintaining this posture until tremor reemerged. If no tremor was recorded after 30 s, patients were considered not to present RET in that particular sample. The procedure was repeated five times, to assure consistency, and pause duration initially measured by visual examination.

Visual examination was performed by an independent rater, blinded to accelerometric measurement, and was performed with a chronograph, which was started when the patient acquired a 90-degree angle position, and was stopped when tremor started to re-emergence. No tremor provocation method was used during this protocol.

Accelerometric recordings were performed using a single axis 0.05–100 Hz bandwidth accelerometer (ATI Pentatek, Buenos Aires, Argentina) at a sample rate of 320 Hz. The accelerometers were taped to the back of each hand, and recordings registered on an ATI Pentatek DB VX8 device (version 1.111.0.0). This method evaluated the summation of tremor contributions in the whole upper extremity.

2.3. Primary objective

To determine levodopa effects on RET pause duration, we compared tremor amplitude at peak frequency on power spectral density (PSD) between the OFF state and best motor score recordings in the defined ON state (lowest MDS-UPDRS score), and correlated results to pause duration.

2.4. Secondary objective

We determined whether correlation existed between MDS-UPDRS postural tremor score (3.15) and RET pause duration. Levodopa effects on the slope of gradual tremor onset after the pause was also investigated. Correlation between degree of response to levodopa and RET pause duration was calculated. In addition, RET pause duration determined by visual examination was compared to results registered with accelerometer and digital analysis.

2.5. Signal analysis

Accelerometer signals recorded were exported and analyzed offline, using BIOPAC AcqKnowledge 4.2.0 software. Power spectral density (PSD) of tremor signal at rest and during posture was analyzed using Fast Fourier Transform (FFT) [15]. Rest tremor spectral analysis results were compared to those from postural tremor, to confirm no significant differences in dominant frequency were present (± 1.5 Hz). Lack of difference was considered indicative of both tremors being manifestations of parkinsonian tremor [2]. Subjects with differences above 1.5 Hz were excluded from further analysis.

Amplitude at peak frequency was also calculated using FFT [15]. First dominant peak frequency in PSD was used for further filtering, applying separate low and high pass filters (FIR Butterworth) at ± 2 Hz of the peak frequency [16]. Accelerometer signal was rectified and smoothed with a smoothing factor of 320 samples (1 s) to generate an envelope, and the resulting signal used for subsequent analysis.

Arm elevation produced a movement-related artifact in the accelerometer signal. Re-emergent tremor pause duration was therefore measured considering the time interval between the end of the artifact and the onset of tremor exceeding the signal amplitude at the start of the position-generated condition [3], as is shown in Fig. 1 This value was then compared to the pause duration determined by visual examination. After tremor suppression with movement, tremor re-emerges gradually. The slope of gradual tremor increase after the pause, expressed in g/s, was calculated.

Postural tremor pause duration (determined both clinically and digitally), amplitude at peak postural tremor frequency and slope were measured in every sample.

2.6. Statistical analysis

Data were normalized to minimize absolute value variability and dispersion. Normalization was performed by dividing the data values by the OFF state values, and expressing them as percentage. Mean scores for amplitude were compared using one-way analysis of variance (ANOVA), repeated measures ANOVA and paired T-test, accordingly. Wilcoxon signed rank test was used to compare pause duration scores. Correlation between absolute values of pause duration, amplitude and MDS-UPDRS scores were correlated using Pearson's or Spearman's correlation, accordingly.

3. Results

Twenty-one patients (mean age 66.63 ± 9.3; 66.7% male) were included in the study and underwent a levodopa challenge, as described previously. Mean MDS-UPDRS Part III scores in OFF and ON state were: 29.19 ± 10.4 and 19 ± 8.12, respectively. Mean duration to achieve the best motor score was 84.76 min, and patients needed to be evaluated 4.62 times on average. Reduction in mean MDS-UPDRS part III score after levodopa challenge was 33.23% ± 17.98%. Three patients were excluded due to coexistence of PD and ET.

Spectral analysis of tremor during OFF state showed a mean tremor frequency of 4.96 ± 0.74 Hz at rest and 5.24 ± 0.84 Hz during sustained posture, with a mean difference between rest and posture of 0.28 ± 0.59 Hz. ON state recordings showed similar frequencies, with 5.15 ± 1.03 Hz at rest and 5.27 ± 0.81 Hz during posture, with a mean difference of 0.20 ± 0.23 Hz. Accelerometer-recorded tremor amplitude at baseline (OFF state) showed a mean decrease of 25.4% ($p = 0.004$) after levodopa administration compared to best motor score (ON state) (Fig. 2).

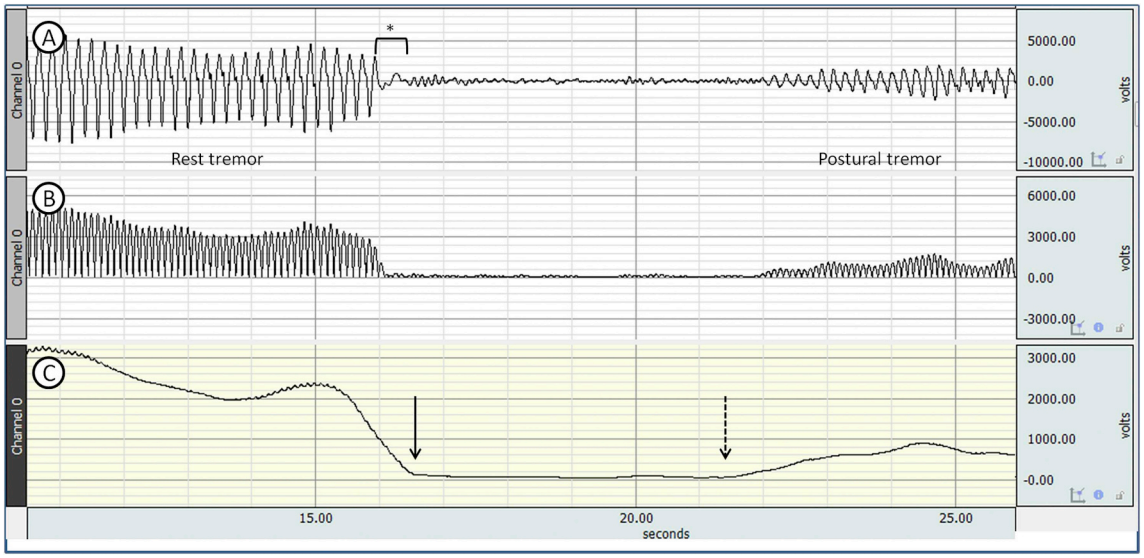

Fig. 1. Tremor signal analysis and measurement of pause duration. The raw signal (A) shows rest tremor activity on left handside, followed by a movement artifact produced by arm elevation (*), a pause, and postural tremor on the right handside. The signal is then filtered and rectified (B), and an envelope is generated (C). The solid arrow marks the onset of postural activity, while the dotted arrow shows the onset of postural tremor.

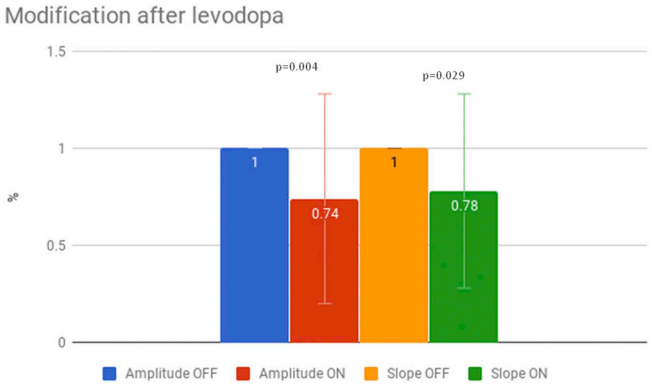

Fig. 2. Modification after levodopa. The graph shows the modification of amplitude at peak frequency and slope between OFF and ON states. Values are expressed in percentage of the baseline value (OFF).

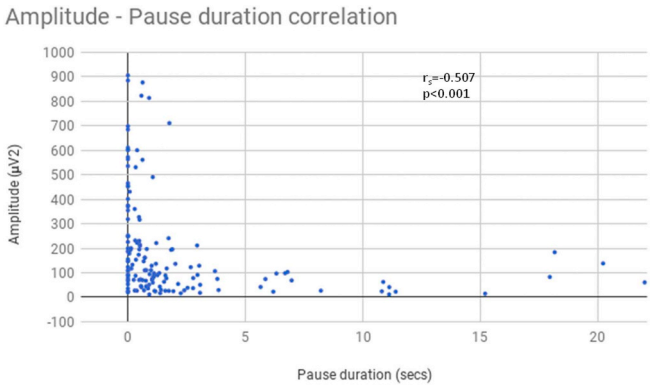

Fig. 3. Amplitude vs pause duration. The figure plots the correlation between amplitude at peak frequency and pause duration.

Spearman's correlation applied to absolute values of RET pause duration and amplitude showed significant inverse correlation between both variables in the OFF state (rs = −0.474, p = 0.030) and ON state (rs = −0.569, p = 0.006), with an overall correlation of rs = −0.507 (p < 0.001) (Fig. 3). Correlation between tremor amplitude, defined by MDS-UPDRS, and RET pause duration, generated a similar result in OFF state (rs = −0.311, p = 0.048) and ON state (rs = −0.503, p = 0.020).

Levodopa exerted a dampening effect on slope gradient: ON state postural tremor slope gradient decreased by 22% compared to OFF state (p = 0.029) (Fig. 2). Comparison between RET pause duration and total MDS-UPDRS Part III score showed an inverse relation between these variables (rs = −0.295, p = 0.009), suggesting higher degree of overall response to levodopa was associated with longer postural tremor pause duration.

Finally, RET pause duration measured by the accelerometer was significantly shorter than duration determined by visual inspection (4.37 ± 5.56 vs 3.35 ± 4.91 s, p < 0.001) (Fig. 4). This was also true when analyzing the percentage of cases in which no pause was observed: 38.07% when assessed with accelerometer, and 31.62% when visually determined (p = 0.271).

4. Discussion

It is commonly seen that levodopa decreases rest tremor amplitude in most cases [17,18], and sometimes postural tremor as well [11,12]. Re-emergent tremor as initially named by Jankovic et al., in 1999 [3], is regarded as an extension of classical parkinsonian rest tremor [8].

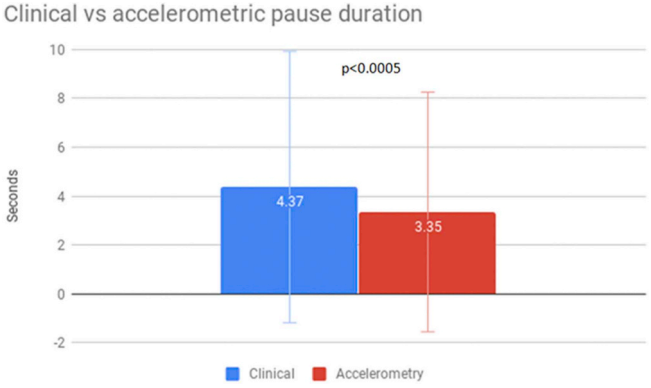

Fig. 4. Clinical vs accelerometric pause duration. The figure shows the comparison between tremor pause duration measured clinically by visual examination and using the accelerometer.

However, it remains to be determined whether RET represents a real pause in rest tremor generation due to movement or acquisition of a posture [2,3,6,19,20].

In this study we observed that RET latency was clearly conditioned by tremor amplitude as well as by recording method sensitivity, since many patients clinically presenting RET were reclassified as having zero RET latency when tremor was measured with an accelerometer.

Some experts have described tremor re-emergence even several minutes after posturing [21], for which our 30-s window might be considered a potential selection bias. However, there is no report, to the best of our knowledge, showing a mean latency of more than 30 s. Therefore, we think that our repeated measures protocol (5-time repetitions every 20 min), might prevent such selection bias.

A recent study by Dirkx et al. [11] evaluated different forms of postural tremor in PD. The most common phenotype found by the authors was re-emergent tremor, characterized by amplitude suppression with posturing, slight frequency difference between rest and postural tremor (0.4 Hz), and clear tremor power decrement in response to dopamine.

Our results are in line with these observations. Additionally, we found strong inverse correlation between RET amplitude and pause duration both in the OFF and ON states. The levodopa-induced decrease in tremor amplitude mentioned, was associated with prolongation in RET pause duration, meaning that with levodopa, tremor amplitude diminishes and the pause gets longer. There is also a slope of the return of the tremor. This slope is more gradual with lower tremor amplitude and likely adds to the clinical impression of a longer duration pause.

Furthermore, our results showed RET can be detected earlier using an accelerometer, and in many cases, patients clinically considered as having reemergence, actually showed continuous low amplitude tremorous activity on accelerometric analysis. However, by the methods used it is impossible to confirm this hypothesis and whether the activity found in the accelerometry corresponds to tremor transmission from other joints cannot be ruled out as differential effects of levodopa on proximal and distal symptoms have been described [22,23].

Few studies have analyzed the electrophysiological characteristics of RET [3,9,11,17,19,20], with most of them designed to detect physiological hallmarks of RET in order to differentiate it from other types of tremor. They therefore focused on frequency analysis, amplitude and pause duration, with their main finding being that the re-emergence phenomenon is highly predictive of PD, and that its physiology is similar to that of classical resting tremor, with a slight decrease in amplitude and increase in frequency. All of them found tremor suppression during movement and posturing. However, to the best of our knowledge, there are no studies analyzing whether tremor activity is truly interrupted during tremor pause or simply decreases in amplitude. In addition, the classical method used to measure RET pause duration is by detecting when tremor amplitude/power exceeds baseline postural activity. This concept is in line with our findings, in which tremor detection, both clinically and neurophysiologically, was determined by tremor amplitude.

In summary, our results show that levodopa-induced re-emergent tremor amplitude dampening is associated with postural tremor pause prolongation, as well as with decreased tremor intensity and velocity of tremor increase. This scenario (low amplitude, intensity and slope gradient) seems to affect pause duration registration, with more precise results obtained using instrumental measuring devices. Pause duration therefore appears to be an amplitude-related phenomenon, as amplitude decrease after levodopa administration led to pause prolongation. We hypothesize that the notion of pause might not derive from an actual central oscillation stop, but by clinical observation, and that pause segments might correspond to low amplitude non-detectable tremor. Therefore, the pause clinically is assessed longer than it really is. Further electrophysiological studies, including EMG measurements, correlating pause and central oscillator activity are needed to address this hypothesis in more detail.

Conflicts of interest

None declared.

Disclosures

None reported.

Declarations of interest

None.

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