Parkinsonism and Related Disorders 25 (2016) 100–103

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Short communication

Tremor pattern differentiates drug-induced resting tremor from Parkinson disease

R. Nisticò [a], A. Fratto [b], B. Vescio [a], G. Arabia [a, b], G. Sciacca [c], M. Morelli [a, b], A. Labate [a, b], M. Salsone [a], F. Novellino [a], A. Nicoletti [c], A. Petralia [d], A. Gambardella [a, b], M. Zappia [c], A. Quattrone [a, b, *]

[a] Neuroimaging Research Unit, Institute of Bioimaging and Molecular Physiology, National Research Council, Germaneto, Catanzaro, Italy
[b] Institute of Neurology, Department of Medical Sciences, University Magna Graecia, Catanzaro, Italy
[c] Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia" University of Catania, Italy
[d] Department of Clinical and Experimental Medicine, University of Catania, Italy

ARTICLE INFO

Article history:
Received 31 August 2015
Received in revised form
27 November 2015
Accepted 1 February 2016

Keywords:
Resting tremor
Drug-induced parkinsonism
Electromyography

ABSTRACT

Objective: DAT-SPECT, is a well-established procedure for distinguishing drug-induced parkinsonism from Parkinson's disease (PD). We investigated the usefulness of blink reflex recovery cycle (BRrc) and of electromyographic parameters of resting tremor for the differentiation of patients with drug-induced parkinsonism with resting tremor (rDIP) from those with resting tremor due to PD.
Methods: This was a cross-sectional study. In 16 patients with rDIP and 18 patients with PD we analysed electrophysiological parameters (amplitude, duration, burst and pattern) of resting tremor. BRrc at interstimulus intervals (ISI) of 100, 150, 200, 300, 400, 500 and 750 msec was also analysed in patients with rDIP, patients with PD and healthy controls. All patients and controls underwent DAT-SPECT.
Results: Rest tremor amplitude was higher in PD patients than in rDIP patients ($p < 0.001$), while frequency and burst duration were higher in rDIP than in PD ($p < 0.001$, $p < 0.003$, respectively). Resting tremor showed a synchronous pattern in all patients with rDIP, whereas it had an alternating pattern in all PD patients ($p < 0.001$). DAT-SPECT was normal in rDIP patients while it was markedly abnormal in patients with PD.
Conclusions: In the absence of DAT-SPECT, the pattern of resting tremor can be considered a useful investigation for differentiating rDIP from PD.

1. Introduction

Drug-induced parkinsonism (DIP) is the second leading cause of parkinsonism in the elderly and general populations, after Parkinson disease (PD). DIP has been associated either with the use of drugs that block dopamine receptors, including antipsychotic agents, antiemetics and calcium channel antagonists, or with the use of some antiepileptic drugs, such as valproic acid [1].

The clinical manifestations of DIP are often indistinguishable from those of PD [2], mainly when DIP show resting tremor (rDIP) and asymmetrical symptoms [1]. Although dopamine transporter (DAT) imaging can differentiate DIP from PD, this procedure cannot be recommended to all patients due to the economic burden and complexity of process [3].

The recovery cycle of the blink reflex (BRrc) is a measure of brainstem excitability.

BRrc has been reported to be enhanced in various movement disorders, such as patients PD [4], but no data exist in patients with DIP. The pattern of resting tremor has been reported to be useful for differentiating patients with PD from those with essential tremor associated with resting tremor (rET) [5].

The aim of the study was to evaluate the possible usefulness of BRrc and of the electromyography parameters of resting tremor for the differentiation of patients with rDIP from those with resting tremor due to PD.

2. Patients and methods

Sixteen patients with rDIP, 18 patients with PD and 20 age- and

* Corresponding author. Institute of Neurology, Department of Medical Sciences, University "Magna Graecia", 88100 Germaneto, Catanzaro, Italy. Tel.: +39 0961 3647071; fax: +39 0961 3647177.
E-mail address: quattrone@unicz.it (A. Quattrone).

http://dx.doi.org/10.1016/j.parkreldis.2016.02.002
1353-8020/

sex-matched control subjects were enrolled in the current study. Among rDIP patients, 5 with psychiatric disorders were taking amisulpiride or olanzapine or perfenazine, 2 with migraine were taking flunarizine, and 9 patients with epilepsy were in valproate therapy. Patients with PD and subjects with rDIP were recruited from the Movement Disorders Unit, while those taking valproate from the of Epilepsy Unit of the University "Magna Graecia" of Catanzaro. rDIP was defined by the following criteria: 1) presence of resting tremor with parkinsonian signs, 2) no history of resting tremor before the use of the offending drug, 3) onset of parkinsonism symptoms with resting tremor during the use of the offending drug [1]. A clinical diagnosis of PD was made according to the Brain Bank Criteria [6]. Six out of 18 PD patients received levodopa and dopamine agonists, 5 received dopamine agonists, 5 received levodopa, 1 received levodopa, selegiline and dopamine agonists, 1 received selegiline and biperidene. PD and rDIP patients without resting tremor were excluded from the study.

rDIP and PD patients were matched for age, sex, onset and duration of the disease (calculated as the time from the appearance of parkinsonian signs), motor disability (UPDRS-ME) and severity of resting tremor (UPDRS-ME, section III, item 20). Each patient underwent an accurate clinical history, a neurological examination, and videotape evaluation .

In all participants, global cognitive status was assessed through the Mini Mental State Examination (MMSE). All participants were examined by neurologists specialized in movement disorders who were blinded to the patient's diagnosis. Imaging studies, including brain magnetic resonance imaging (MRI) and ^{123}I-FP-CIT-SPECT (DAT-SPECT), were assessed in all patients and control subjects. No subject had any history of thyroid diseases, cerebrovascular diseases, other degenerative neurological diseases or intracranial lesions in brain MRI. No control subject received anti-parkisonian medication and offending drug. In PD patients, all tests were performed in off state requiring the patients not to take anti-parkinsonian therapy from midnight prior to the examination.

Resting tremor was clinically assessed as present or absent; it was not marked as present if the limb did not appear to be fully at rest. All patients underwent an electrophysiological study for resting tremor analysis and BRrc. The upper limb with dominant tremor was recorded. Rest measurements were performed with the patient's arm flexed at 90°, fully supported against gravity. The tremor activity was recorded by 2 pairs of surface and needle electrodes from the antagonistic groups of muscles of the forearm as described elsewhere [5].

For the BRrc recording, we followed the description by Kimura [7]. All stimuli were 0.2 msec duration. We investigated diverse stimulus intensities (between 5 and 30 mA) choosing those which were 3 times the threshold of the blink reflex responses. BRrc was assessed at interstimulus intervals (ISIs) of 100, 150, 200, 300, 400, 500, and 750 msec. For each ISI, the R2 area ratio (R2 area of conditioned response divided by the R2 area of unconditioned response) was calculated.

Before inclusion in the study, written informed consent was obtained from all participants, and the study was approved by the institutional review board.

2.1. Statistical analysis

Differences in sex distribution have been assessed by means of the Fisher's exact test. The Shapiro–Wilk test was used to check for normality before performing comparisons. The Mann–Whitney U test was used to assess differences in age at onset, UPDRS-ME score, disease duration, tremor burst and phase offset, while tremor amplitude and frequency were compared by means of the t-test. Age at examination and DAT-SPECT imaging were compared using the Kruskal–Wallis test followed by the pairwise Wilcoxon rank sum test with Bonferroni correction.

Significant differences of 5% between patients with rDIP, patients with PD and controls were calculated using pairwise t-tests corrected according to Bonferroni. Sensitivity, specificity and accuracy were determined for differentiating rDIP patients from PD patients, evaluating optimal cut-offs for tremor amplitude, burst, frequency, phase difference, DAT-SPECT and R2 recovery at ISI 100 on Receiver Operating Characteristic (ROC) curves. The optimal cut-off levels were defined as the values with the maximum sum of sensitivity and specificity. Statistical analysis was performed with R Statistical Software (R for Unix/Linux, version 2.15.1, the R Software Foundation for Statistical Computing, 2012).

3. Results

Clinical, demographic and DAT-SPECT data of patients and controls are shown in Table 1. Four out of 16 rDIP patients discontinued the drug after clinical and electrophysiological

Table 1
Demographic, clinical and imaging characteristics.

Characteristic	rDIP (n = 16)	PD (n = 18)	CTRL (n = 20)	*p*-value
Age (mean ± SD)	68.8 ± 10.33	67.7 ± 6.25	68.5 ± 8.85	NS[a]
Woman, n. (%)	13 (81%)	16 (89%)	13 (65%)	NS[b]
Age at onset (mean ± SD)	64.19 ± 8.96	63.56 ± 6.09		NS[c]
Duration of disease (mean ± SD)	5.50 ± 4.37	4.16 ± 2.73		NS[c]
MMSE (mean ± SD)	24.89 ± 2.98	25.79 ± 3.38		NS″
UPDRS-ME (mean ± SD)	20.75 ± 11.96	22.33 ± 9.79		NS[c]
UPDRS-ME item 20 (mean ± SD)	4.31 ± 1.81	4.67 ± 2.74		NS[c]
DAT-SPECT				
Left putamen	4.21 ± 0.74	2.57 ± 0.74	4.19 ± 0.39	*<0.0001*[a]
Right putamen	4.30 ± 0.65	2.61 ± 0.76	4.29 ± 0.34	*<0.0001*[a]
EMG rest tremor recording				
Frequency Hz (mean ± SD)	5.92 ± 0.72	4.69 ± 0.37		*<0.0001*[d]
Amplitude mV (mean ± SD)	0.16 ± 0.08	0.41 ± 0.20		*<0.0001*[d]
Burst duration ms (mean ± SD)	103.51 ± 14.8	88.76 ± 11.02		*0.026*[c]
Phase degree (mean ± SD)	20.88 ± 16.03	174.84 ± 34.49		*<0.0001*[c]

[a] Kruskal–Wallis test followed by pairwise Wilcoxon rank sum test with Bonferroni correction (left and right putamina: DIP vs. CTRL, p = NS; PD vs. CTRL, $p < 0.0001$; PD vs. DIP, $p < 0.0001$).
[b] Fisher's exact test.
[c] The Mann–Whitney U test.
[d] t-test.