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Original Article

Time structure of leg movement activity during sleep in untreated Parkinson disease and effects of dopaminergic treatment

Monica Puligheddu [a], Michela Figorilli [a], Debora Aricò [b], Alberto Raggi [c], Francesco Marrosu [a], Raffaele Ferri [b,*]

[a] Sleep Center – Neurophysiology Unit, University of Cagliari, Monserrato (CA), Italy
[b] Department of Neurology, Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Troina, Italy
[c] Neurology Unit, Morgagni-Pierantoni Hospital, Forlì, Italy

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ABSTRACT

Objectives: To evaluate the specific time structure of periodic leg movements during sleep (PLMS) in untreated Parkinson disease (PD) patients by means of an advanced analysis; and to evaluate the effects of treatment on this activity, in a cross-sectional comparison and in a prospective follow-up study, in a subgroup of previously untreated patients.

Methods: Forty-four consecutive PD patients were enrolled in the study; 19 had not yet started any drug therapy for PD (PDnother); 10 out of these patients were re-evaluated after an average time lag of 19.6 months from baseline. The remaining 25 patients (PDther) were taking L-dopa and/or dopamine agonists. Eighteen age-matched normal controls were also included. All subjects underwent a polysomnographic recording and the time structure of their sleep leg movement activity was analyzed by means of the periodicity index and other advanced measures.

Results: Both PD groups tended to show increased PLMS and decreased isolated limb movement activity with respect to controls. PLMS index >15/h was found in 26.3% of PDnother patients, 24.0% of PDther subjects, and in 16.7% of controls; none of the three PDnother patients who had PLMS index >15/h at baseline sustained this level at follow-up, nor did the other seven patients. The intermovement interval distribution showed a clear peak at 10–40 s in the PDnother group; a suppression of this peak was observed after the introduction of dopaminergic treatment in the subgroup of 10 PDnother patients. Both groups of PD patients showed a progressively decreasing number of PLMS through the night; an almost complete abolition of PLMS was seen in the first 2 h of sleep after the introduction of dopaminergic drug therapy.

Conclusion: Our data do not seem to support the hypothesis that PLMS are particularly frequent in PD but seem to indicate an interaction between PD pathophysiology and genetic predisposition for PLMS, producing a slightly increased number of patients with this sleep motor phenomenon when compared to controls.

1. Introduction

The presence of sleep disorders in Parkinson disease (PD) was reported by James Parkinson in 1817 when he published "An essay on the shaking palsy" [1]. At least three-quarters of PD patients have sleep problems: two-thirds of them have problems in initiating sleep; difficulties maintaining sleep are reported by nine out of ten; and 50% spontaneously refer sleep problems [2,3]. The most frequent sleep disturbances in PD are difficulty initiating sleep, frequent night-time awakening and sleep fragmentation, nocturia, restless legs syndrome (RLS)/periodic limb movements during sleep (PLMS), sleep breathing disorders, drug-induced symptoms, narcolepsy-like features, sleep attacks and excessive daytime sleepiness, and parasomnias associated with rapid eye movement (REM) sleep [2].

Some past studies have indicated that periodic leg movements during sleep (PLMS) are especially increased in PD [4,5]; a more recent review of case–control studies of sleep in PD [6] has listed two studies confirming this increase [7,8] and five which did not find changes [9–13]. However, their analysis has been based on

* Corresponding author. Address: Sleep Research Centre, Department of Neurology I.C., Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Via C. Ruggero 73, 94018 Troina, Italy. Tel.: +39 0935 936111; fax: +39 0935 936694.
E-mail address: rferri@oasi.en.it (R. Ferri).

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the computation of the PLMS index (number of PLMS/h of sleep) alone. This measure is largely insufficient to describe the real periodicity of the leg movement activity during sleep and is unspecific [14]. In recent years, a more advanced approach has enabled a more accurate description of periodicity and other time-structure features of leg movements during sleep in RLS [15–17] and other clinical conditions in which PLMS have been reported, such as REM sleep behavior disorder (RBD) [18], narcolepsy [19], and insomnia [20]. The application of this method has found significant differences between the different clinical conditions that the PLMS index alone failed to detect [14] and has enabled assessment of the effects of drug therapy with great accuracy [21,22].

For the reasons listed above, the aims of this study were: (i) to evaluate the specific time structure of PLMS in untreated PD patients by means of an advanced analysis; (ii) and to evaluate the effects of treatment on this activity in a cross-sectional comparison first, and, in a prospective follow-up study, in a subgroup of previously untreated patients.

2. Methods

2.1. Subjects

Forty-four consecutive PD patients were enrolled in the study [28 men and 16 women; mean (SD) age, 67.6 (7.0) years]. All patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD [23]. Exclusion criteria were: presence of other neurological diseases, Mini-Mental State Examination score <20 [24], and presence of a psychiatric disease according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) [25]. The Hoehn & Yahr (H&Y) disease stage was assessed for each patient [26] and disease duration was carefully evaluated.

Nineteen patients had not yet started any drug therapy for PD (PDnother subgroup), including 11 males and eight females [mean (standard deviation) age, 67.6 (6.2) years]. Ten of these patients (seven males and three females), were re-evaluated after an average time lag of 19.6 (10.8) months from the first (baseline) assessment; the remaining nine patients refused the second polysomnographic night recording or were unavailable.

The remaining 25 patients [17 men and eight women; mean age, 67.6 (7.7) years] constituted the PDther subgroup and were taking L-dopa monotherapy, dopamine agonist alone, or a combination of the two. In order to evaluate different dopaminergic treatments, drug dosages were converted to L-dopa dosage equivalents (LEDs), according to Tomlinson et al. [27]. None of the patients was taking antidepressants and only two of them were taking clonazepam at bedtime; however, this substance does not seem to affect PLMS [28].

A careful diagnosis of RBD was also carried out, based on the International Classification of Sleep Disorders, 2nd ed. [29] criteria for RBD, and including the presence of REM sleep without atonia, sleep-related injurious–disruptive behaviors by history or abnormal sleep behaviors documented during polysomnographic monitoring, and absence of electro-encephalographic (EEG) epileptiform activity during REM sleep. Also the presence of RLS was assessed following standard criteria [29].

The control group was formed by 18 age-matched normal controls [11 men and seven women aged 66.9 (8.1) years]. The exclusion criteria for the control group were the same as described for PD patients; additionally, the presence of subjective sleep complaints (insomnia, daytime sleepiness, RLS, RBD symptoms, snoring, or witnessed apnea) was also ruled out. None of the controls was taking hypnotics or benzodiazepines.

This study was approved by the local ethics committee and all subjects provided informed consent according to the Declaration of Helsinki before entering the study.

2.2. Polygraphic sleep recordings

Each subject underwent a full polysomnographic night recording, after an adaptation night, carried out in a standard sound-attenuated (noise level to a maximum of 30 dB nHL) sleep laboratory. Subjects were not allowed to have beverages containing caffeine during the afternoon preceding the recording and were allowed to sleep until their spontaneous awakening in the morning.

The following parameters were included in the polysomnographic study: EEG (at least three channels – one frontal, one central, and one occipital – referred to the contralateral earlobe); electro-oculogram (electrodes placed 1 cm above the right outer cantus and 1 cm below the left outer cantus and referred to A1), electromyogram (EMG) of the submentalis muscle, EMG of the right and left tibialis anterior muscles (bipolar derivations with two electrodes placed 3 cm apart on the belly of the anterior tibialis muscle of each leg), and electrocardiogram (one derivation). The sleep respiratory pattern of each patient was assessed by means of oral and nasal airflow (thermistor and/or nasal pressure cannula), thoracic and abdominal respiratory effort (strain gauge), and oxygen saturation (pulse-oximetry) in a previous recording (within one week) or during the study night. Sleep signals were stored on hard disk in European data format for further analysis.

2.3. Sleep scoring and detection of limb movements

Sleep stages were scored following standard criteria [30] on 30 s epochs by means of the sleep analysis software Hypnolab 1.2 (SWS Soft, Italy). Leg movements (LMs) during sleep were first detected by the same software. With this software, the detection is performed by means of a human-supervised automatic approach controlled by the scorer. The performances of this system have been evaluated and validated [31]; for this study, one scorer (R.F.) visually edited the detections proposed by the automatic analysis before the computation of the LM parameters, which were automatically generated by the same software, adopting the criteria set by the International RLS Study Group and endorsed by the World Association of Sleep Medicine [32]. The PLMS index was calculated as the number of LMs included in a series of four of more, separated by >5 s and <90 s, per hour of sleep. Additionally, the number of intermovement intervals of 10–90 s, all in sequences of at least three, was divided by the total number of intervals to yield the periodicity index; this index can vary between 0 (absence of periodicity, with none of the intervals being 10–90 s) and 1 (complete periodicity, with all intervals being 10–90 s) [15,33]. The periodicity index is independent of the absolute number of LMs recorded and calculated for all nights included in this study.

2.4. Statistical analysis

All comparisons were performed using one-way analysis of variance (ANOVA), followed by the least significant difference test for post-hoc analyses, or by Student's *t*-test for paired datasets, as appropriate. However, because of the limited number of subjects available for the follow-up analysis, and to rule out possible type II errors, we also calculated effect sizes using Cohen's *d*-value which is defined as the difference between two means divided by their pooled standard deviation. According to Cohen, 0.2 indicates a small effect, 0.5 a medium effect, and $\geqslant$0.8 a large effect. The χ^2-test was used for the comparison of frequencies. The commercially available Statistica software package (StatSoft, Inc., 2001;