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SLEEP MOTOR ACTIVITY IN PARKINSONIAN SYNDROMES AT ONSET: A PROSPECTIVE STUDY TO DETERMINE POTENTIAL DIAGNOSTIC AND PROGNOSTIC MARKERS

Presentata da: **DOTT.SSA MARIA ALESSANDRIA**

Coordinatore Dottorato **Relatore**

PROF. SANDRO MATTIOLI **PROF. PIETRO CORTELLI**

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1. INTRODUCTION

1.1. PARKINSON'S DISEASE AND PARKINSONISMS: DIFFERENTIAL DIAGNOSIS

Parkinsonism is defined by the association of bradykinesia with either hypertonia, resting tremor, or postural instability. The main cause of parkinsonism is idiopathic Parkinson's disease (PD), a neurodegenerative disorder with a progressive (but not exclusive) loss of dopaminergic neurons. PD is characterized by asymmetrical parkinsonism, progressive worsening and initial benefit from levodopa. PD is primarily a disease of the elderly. Its prevalence increases with age from about 0.9% among persons 65 to 69 years old to 5% among persons 80 to 84 years old, with a slight male preponderance (de Rijk et al, 1997). Only a small percentage of patients, mostly with the genetic forms of PD, develop parkinsonism before the age of 45 years. In the absence of a reliable diagnostic marker, the clinical diagnosis of PD is based on the presence of characteristic features. Several diagnostic criteria have been developed for PD, including the U.K. Parkinson's Disease Society Brain Bank criteria used in various clinical-pathologic studies (Hughes et al, 1992 a) (Hughes et al, 1992 b). In 1999, a set of diagnostic criteria for PD was proposed, based on a review of the literature regarding the sensitivity and specificity of the characteristic clinical features (Gelb et al, 1999). The reliability of the different diagnostic criteria, however, has not been vigorously tested by autopsy examination, which is commonly considered the gold standard. Two separate clinical-pathologic series concluded that only 76% of patients with a clinical diagnosis of PD actually met the pathologic criteria; the remaining 24% had evidence of other causes of parkinsonism. One of the studies was based on autopsied brains collected from 100 patients who had been clinically diagnosed with PD by the U.K. Parkinson's Disease Society

Brain Bank (Hughes et al, 1992 a) (Hughes et al, 1992 b), and the other study consisted of autopsy examinations of brains from 41 patients who were followed prospectively by the same neurologist over a 22-year period (Rajput et al, 1991). In a study of 143 cases of parkinsonism that came to autopsy and had a clinical diagnosis made by neurologists, the positive predictive value of the clinical diagnosis was 98.6% for PD and 71.4% for the other parkinsonian syndromes (Hughes et al, 2002). In the DATATOP study, 800 patients were prospectively followed by trained parkinsonologists from early, untreated stages of clinically diagnosed PD for a mean of 7.6 years (Jankovic et al, 2000). An analysis of autopsy data, imaging studies, response to levodopa, and atypical clinical features indicated an 8.1% inaccuracy of initial diagnosis of PD by Parkinson experts. Although this is considerably less than the diagnostic error rate reported previously, the final diagnosis was not based on pathologic confirmation in all cases. In another study on a small cohort of patients, clinical diagnosis had changed in 33% of patients after a median follow-up of 29 months. Most (82%) changes occurred in the first year and were due to the development of atypical clinical features, particularly early cognitive impairment; the results of brain imaging; responsiveness to levodopa; and the rate of disease progression (Caslake et al, 2008). Much of the difficulty in the diagnosis of PD is in differentiating it from other disorders that cause parkinsonism. These include other neurodegenerative disorders such as dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal degeneration (CBD) and non-degenerative causes such as vascular parkinsonism or drug induced parkinsonism (e.g., as a result of antidopaminergic drugs). Features particularly useful in differentiating PD from other parkinsonian disorders include: absence or paucity of tremor, early gait abnormality (such as freezing), postural instability, pyramidal tract findings and poor response to levodopa. Therefore, while improvement with levodopa supports the diagnosis of PD, response to levodopa cannot be reliably used to differentiate PD from

atypical parkinsonisms. At disease onset, the evolution of different features can be quite variable and, consequently, the differential diagnosis of each form of parkinsonism and its prognosis is often difficult for clinicians. Changing between different parkinsonian syndromes will alter what information is given to the patient about prognosis. Further research, in larger groups and over longer periods, is necessary to identify factors that may improve the accuracy of diagnosis at the initial assessment.

1.2. SLEEP DISTURBANCES IN PD AND ATYPICAL PARKINSONISMS

Neurodegenerative disease characterized by parkinsonism may present a variety of non-motor features, such as sleep disturbances, cognitive impairment, autonomic dysfunctions and olfactory deficit. Sleep disturbances are common non-motor symptoms in parkinsonian patients. The prevalence of sleep disorders in PD is reportedly 40% to 90% (Suzuki et al, 2011). The sleep disturbances observed in patients are not specific to PD and include insomnia, excessive daytime sleepiness (EDS), sleep-disordered breathing (SDB), restless legs syndrome (RLS), periodic leg movements during sleep (PLMS) and rapid eye movement (REM) sleep behaviour disorder (RBD). Sleep problems in PD and atypical parkinsonisms are multifactorial and the mechanisms of the sleep disturbances are not fully known, but they probably include a clear interaction between drug and disease. Mechanisms of sleep disturbances in patients include rigidity and bradykinesia hindering turning in bed, the effects of dopaminergic medications, age-related changes, and changes integral to the disease itself. Dopaminergic drugs are known to have sleep-inducing properties at low doses while promoting wakefulness at high doses (Chaudhuri and Logishetty, 2009). Changes in the brainstem may occur early in the course of disease, affecting neurotransmitters that play a role

in arousal and wakefulness. Sleep problems are more common and more severe in atypical parkinsonisms than in PD.

1.2.1. INSOMNIA

Insomnia is defined as a recurrent difficulty falling asleep or staying asleep, with daytime psychological or cognitive consequences (International Classification of Sleep Disorders - ICSD, 2005). Insomnia is common in all forms of parkinsonism. A community-based survey determined that 60.3% of patients with PD had a sleep problem, a substantially higher proportion than in patients with diabetes mellitus (45%), or in elderly controls (33%) (Tandberg et al, 1998). As many as 52.5% of patients with MSA have complained of sleep fragmentation, compared to 38.7% patients with PD (Ghorayeb et al, 2002). The most severe and specific insomnia is observed in patients with PSP (Arnulf et al, 2005) (Sixel-Döring et al, 2009). Sleep monitoring does not provide additional information on the cause of insomnia in parkinsonian patients, except for a specific, severe decrease of REM sleep in patients with PSP (Montplaisir et al, 1997). Insomnia is a non-specific symptom that does not necessarily result from a selective lesion in any sleep system, except in the case of PSP, in which brainstem cholinergic lesions can encompass the REM sleep executive systems (De Cock et al, 2008). The frequency of insomnia increases with advanced motor stages of PD and a need for a higher daily dose of dopaminergic therapy, an indicator of dopamine denervation. Indeed, slowed movements during the night, difficulties turning in bed, pain, cramps, nocturnal and early morning dystonia, and a frequent need to pass urine, are reported by patients with advanced PD as the main cause of their insomnia (De Cock et al, 2008). The majority of studies show no increase in arousal in PD patients, while nocturnal awakenings may be increased in PD and are influenced by dopaminergic drugs (Peeraully et al, 2012).

General factors, such as aging, anxiety, and depression, can account for some nocturnal sleep disruption in PD. Poor sleep quality correlates with depression and anxiety scores (Borek et al, 2006).

1.2.2. EXCESSIVE DAYTIME SLEEPINESS

EDS is defined as a disabling trend to doze or fall asleep in various circumstances (e.g. reading, as a passenger in a car, during a meeting) that interferes with family, professional, and social life. Daytime sleepiness in PD can be self-reported, but is better referred by caregivers, because some patients are unaware of being abnormally sleepy. Case-control epidemiological studies performed in various countries consistently found higher sleepiness scores and a higher incidence (range 16-74%, but usually around 33%) of abnormal somnolence in PD patients than in age-matched and sex-matched controls (De Cock et al, 2008). EDS is associated with more advanced disease, higher doses of levodopa-equivalent, and sometimes the use of dopamine agonists (De Cock et al, 2008). The most worrying aspect of sleepiness in PD is sleep attacks, or sudden onsets of sleep without prodrome, first been described in patients using the new non-ergot dopaminergic drugs pramipexole and ropinirole (Frucht et al, 1999). Examples of sleep attacks include patients falling asleep during stimulating life conditions, such as eating a meal (the head drooping over the plate), walking, at work, carrying a child on an escalator, and, the most dangerous situation, while driving a car. The percentage of PD patients having experienced sleep attacks varies from 1 to 14%, and 1% to 4% PD patients report having experienced sleep attacks while driving (De Cock et al, 2008). A “narcolepsy-like” pattern of sleepiness (multiple sleep-onset REM periods) was found in PD: in a series of 54 PD patients, Arnulf et al found that more than half would fall asleep within, on average, 5 minutes, indicating pathological sleepiness; moreover, 41% of

sleepy patients fell directly into REM sleep at least twice, an abnormal pattern mostly observed in primary narcolepsy (Arnulf et al, 2002). The mechanisms of sleepiness and sleep attacks in PD can include a complex drug-and-disease interaction. Most arousal systems are affected by neuronal loss and Lewy bodies in PD brains, including the norepinephrine neurons in the locus coeruleus, the serotonin neurons in the raphe, the cholinergic neuron in the basal forebrain, and the hypocretin (orexin) neurons (also affected in primary narcolepsy) in the hypothalamus. By contrast, the wake-active dopamine neurons in the ventral periaqueductal grey matter and the histamine neurons in the hypothalamus are intact in PD brains (De Cock et al, 2008). In PD, sleepiness may be more common in patients with advanced disease. Sleep apnoea, PLMS, and sleep fragmentation do not correlate with the severity of daytime sleepiness, suggesting they do not contribute much to the mechanisms of sleepiness. The use of dopaminergic drugs exposes PD patients to a twofold to threefold higher risk of sleep attacks and points toward the sedative role of dopamine agonists in some PD patients. The risk of sleep attacks is similar using ergot agonists (bromocriptine, pergolide) or non-ergot agonists (pramipexole, ropinirole). The risk increases with higher daily dosage and decreases with drug withdrawal. By contrast, levodopa is more rarely sedative. Why drugs that are supposed to stimulate the alerting brain system (and do so when given at bedtime) are, on the contrary, sedative is as yet unknown. This effect cannot be explained, at these high doses, by the biphasic effect (presynaptic sedative effect at low dose, postsynaptic alerting effect at high dose) of dopamine agonists described in animals (De Cock et al, 2008). The sedation observed in selective PD patients suggests a genetic vulnerability to this side-effect of dopamine agonists, although sleepiness does not correlate with genetic variants of the enzyme responsible for dopamine catabolism (Arnulf et al, 2005) (De Cock et al, 2008). EDS may also affect patients with atypical parkinsonism, such as DLB, MSA, and PSP. The SLEEMSA study (Moreno-López et al, 2011) compared consecutive MSA patients

with PD patients and healthy subjects, matched for age and sex, to assess the frequency and associations of EDS in MSA. EDS was present in 28% of patients with MSA, 29% of patients with PD, and 2% of healthy subjects. Unlike PD, the amount of dopaminergic treatment in MSA was not correlated with EDS. Disease severity was weakly correlated with EDS in MSA and PD. RLS occurred in 28% of patients with MSA, 14% of patients with PD, and 7% of healthy subjects. Multiple regression analysis showed that SDB and sleep efficiency predicted EDS in MSA and the amount of dopaminergic treatment and presence of RLS in PD (Moreno-López et al, 2011). A "narcolepsy-like" pattern of sleepiness (multiple sleep-onset REM periods) was also found, although less frequently than in PD, in some cases of MSA and DLB, but not in PSP (Arnulf et al, 2005) (De Cock et al, 2008).

1.2.3. SLEEP BREATHING DISORDERS

Sleep apnoea has been inconsistently associated with PD. In early, untreated PD, the occurrence of sleep apnoea did not differ from that in normal age-matched controls (Ferini-Strambi et al, 1992) (Wetter et al, 2000), and 31% of patients with PD assessed by polysomnography were shown to have sleep apnoea (Ferini-Strambi et al, 1992). Among 54 sleepy patients with more advanced PD referred to a sleep laboratory, 20% had moderate to severe sleep apnoea (Arnulf et al, 2002). Comparing a series of 100 PD patients (50 unselected consecutive patients matched for age, sex and body mass index and 50 patients referred for sleepiness) with 50 in-hospital controls, all evaluated by video-polysomnography (VPSG), sleep apnoea (defined as an apnoea-hypopnoea index greater than 5) was less frequent in the PD group (27%) than in the control group (40% in-hospital controls). Furthermore, only 10% of all PD patients had severe sleep apnoea. Sleep apnoea was not associated with increased sleepiness, nocturia, depression, cognitive impairment or

cardiovascular events in PD patients. Patients with PD did not display sleep hypoventilation, stridor or abnormal central sleep aponea (De Cock et al, 2010). These frequencies, obtained in a large group of PD patients followed in a tertiary care Movement Disorders Unit, are lower than those obtained in three smaller series, showing that 10/15 patients (Maria et al, 2003), 21/49 patients (Diederich et al, 2005) and 7/9 sleepy patients (Dhawan et al, 2006) had sleep apnoea. These series include patients specifically referred for sleep monitoring, while 50 of De Cock's unselected patients were consecutively recruited without selection bias. Although it is not clear whether obstructive sleep apnoea is more common in PD than in age-matched controls, it is of interest that most studies reporting sleep apnoea note that the body mass index (BMI) of patients with PD who have obstructive sleep apnoea/hypopnoea syndrome (OSAS) is not increased (Arnulf et al, 2002) (Diederich et al, 2005), in contrast to the general population in which an increased body mass index is a strong predictor for obstructive sleep apnoea (Schäfer et al, 2002). SDB may be less prevalent in PD than in other parkinsonian disorders like MSA in which OSAS occurs in 15% to 37% of the cases (Ferini-Strambi and Marelli, 2012) (Vetrugno et al, 2004). In MSA, many of areas involved in the automatic control of respiration are damaged (Benarroch, 2003) and the damage may cause central sleep apnoea, Cheyne–Stokes respiration during sleep and wakefulness, dysrhythmic breathing patterns, such as cluster breathing with periods of apnoea, apneustic breathing, and periodic inspiratory gasps. The stridor, that consists in an upper airway obstruction of the glottic aperture in the larynx because of partial or complete vocal cord abduction restriction, has been reported in 30%–42% of MSA cases (Iranzo et al, 2000) (Vetrugno et al, 2004) (Glass et al, 2006). Sleep apnoea is also frequent in DLB, in which OSAS occurs in 15% to 55% of cases (Terzaghi et al, 2013) (Pao et al, 2013).

1.2.4. REM BEHAVIOUR DISORDER

RBD is a parasomnia characterized by vigorous dream-enacting behaviours, associated with nightmares and abnormal increased phasic and/or tonic electromyographic (EMG) activity during REM sleep (Iranzo et al, 2009) (Boeve, 2010). According to the second edition of the ICSD, a clinical diagnosis of RBD can only be made when a patient displays violent, potentially violent or sleep-disruptive dream-enactment behaviour along with REM sleep without atonia (RWA) as determined by VPSG. RBD may be idiopathic (iRBD) or secondary to neurological diseases, particularly those with involvement of the brainstem such as MSA, PD and DLB. In patients with neurodegenerative disorders, the onset of RBD may either antedate or follow the onset of parkinsonism, cerebellar syndrome, dysautonomia, and cognitive impairment. Several studies have shown that patients with iRBD have an increased risk of developing neurodegenerative diseases such as parkinsonism or dementia, with risk estimates of 20% to 45% after 5 years (Iranzo et al, 2006) (Postuma et al, 2009) (Sixel-Döring et al, 2011). RBD often antedates the full-blown clinical presentation of several neurodegenerative diseases, suggesting that this sleep disorder should be considered part of the neurodegenerative process rather than a predisposing factor (Iranzo et al, 2009). The exact cause of RBD in parkinsonism is mostly unknown, but a non-dopaminergic lesion of the system controlling atonia during REM sleep is highly suspected (Boeve et al, 2007).

1.2.4.1. RBD in PD

When diagnosis is based solely on clinical history, the prevalence of RBD in PD varies from 15% to 46% (Iranzo et al, 2009). When diagnosis of RBD is established using clinical and VPSG criteria, the prevalence of RBD in PD patients ranges between 46% and 58% (Iranzo et

al, 2009). The Montreal group demonstrated that 33% of consecutive unselected patients with PD met the diagnostic criteria of RBD based on VPSG (Gagnon et al, 2002). Recently, 46% of a cohort of 457 PD patients with sleep disturbances was found to have RBD (Sixel-Döring et al, 2011). Most of these studies involved patients in different stage of disease and who had already been treated with dopaminergic drugs. Plomhause and colleagues reported on the frequency of RBD in newly diagnosed dopaminergic treatment-naïve PD patients: in their sample of 57 patients, 30% met the criteria for RBD (Plomhause et al, 2013), demonstrating that RBD is common early in the course of PD. The main strength of this study was its focus on analysing newly diagnosed PD patients prior to dopaminergic treatment with a relatively short duration of parkinsonism, with an average of 11 months and 15 months in PD-RBD and PD-no RBD patients, respectively, in contrast to previous studies with an average of PD duration over five years. Additional strengths included rigorous dual-night VPSG controlling for first-night effect and the use of well-accepted standardized methods for quantifying RWA metrics. Another study involving 20 consecutive patients with untreated early PD found a significantly higher percentage of RWA in PD patients compared to controls, but RBD was diagnosed in only one patient (Bušková et al, 2011). A prospective longitudinal single center observational cohort study of de novo PD patients and matched neurologically healthy controls investigating non-motor features and potential biomarkers in PD ("DeNoPa cohort") showed that 40/158 PD patients (25%) and 2/110 controls (2%) had RBD. This large study identified a significantly higher prevalence of movement events in REM sleep (all motor behaviours and/or vocalizations with a purposeful component, seemingly expressive of a subject's mentation, classified as "REM sleep behavioural events", including minor movements such axial movements, small movements in the distal extremities, facial movements with or without vocalizations as well as violent behaviours) in PD patients (51%) compared to controls (15%), not yet fulfilling the entire spectrum of violent RBD or

classification of RBD according to ICSD (Mollenhauer et al, 2013). Literature data suggest that RBD may be associated with a specific RBD subtype. Patients with the tremor-predominant form of PD (usually a more benign form of the disease) have RBD less often than those with the bradykinetic-hypertonia form (Postuma et al, 2008). Several teams examined the question of whether patients with PD plus RBD would be more cognitively impaired than those without RBD. Numerous cross-sectional studies have shown that patients with RBD have increased cognitive impairment on neuropsychological testing. Among 110 patients with PD, the subgroup with clinical RBD had impaired executive functioning, compared to the group without RBD or hallucinations. This cognitive decline was more marked (with additional impairment of memory and logical abilities) in the presence of hallucinations (Sinforiani et al, 2006). A recent prospective study found that RBD was associated with an increased risk of dementia (Postuma et al, 2012). All patients had a VPSG at baseline. Over a mean 4-year follow-up, the incidence of dementia was assessed in those with or without RBD at baseline using regression analysis, adjusting for age, sex, disease duration, and follow-up duration; 42 patients were included in the full analysis. Twenty-seven patients had baseline RBD, and 15 did not. Four years after the initial evaluation, 48% with RBD developed dementia, compared to 0% of those without. All 13 patients who developed dementia had mild cognitive impairment on baseline examination. RBD at baseline also predicted the new development of hallucinations and cognitive fluctuations (Postuma et al, 2012). Moreover, PD patients with RBD tended to have specific motor and non-motor manifestations, especially orthostatic hypotension (Postuma et al, 2008) (Romenets et al, 2012). This indicates that RBD may be a marker of a relatively diffuse, complex subtype of PD. In PD, the brain structures modulating REM sleep such as the gigantocellularis reticularis nucleus, subcoeruleus region and amygdala are damaged, reflecting the high prevalence of RBD in this disease. The finding that RBD frequently occurs in the rigid-akinetic subtype of

disease may suggest that the ventrolateral region of the substantia nigra pars compacta is more severely damaged in these PD patients (Jellinger, 1999) (Iranzo et al, 2009).

1.2.4.2. RBD in parkinsonisms

RBD in MSA

Most patients with MSA have RBD with a prevalence of 90.5-100% (Plazzi et al, 1997) (Iranzo et al, 2009). RBD is currently considered a red flag for the diagnosis of MSA (Gilman et al, 2008), and may be the first symptom of MSA. One study of 27 RBD patients found that RBD preceded the waking motor symptoms in 12 (44%) (Plazzi et al, 1997). Typically, VPSG shows a marked increase in submental tonic EMG activity during REM sleep which is greater than in iRBD and PD (Iranzo et al, 2009). In addition, phasic EMG activity is usually excessive in REM sleep. Brief episodes of sudden trunk and limb jerks during non-REM sleep were observed in a few MSA subjects with RBD, similar to but less complex than those occurring in the same patients during REM sleep (Iranzo et al, 2009). Aperiodic and periodic limb movements and excessive fragmentary myoclonus are also frequent in non-REM sleep. These non-REM sleep motor abnormalities in MSA patients with RBD are indicators of dissociated states of sleep, in which components of one state intrude into another (Iranzo et al, 2009) (Vetrugno et al, 2009). The finding that brainstem cell loss in MSA is consistent and severe may explain the high prevalence of RBD in this disease.

RBD in DLB

RBD is very common (approximately 70%) among patients with DLB and usually precedes the onset of dementia (Iranzo et al, 2009). The current consensus criteria for DLB consider RBD a suggestive feature of the disease (McKeith et al, 2005). The presence of RBD in a

patient with dementia supports the diagnosis of DLB against AD and other forms of cognitive impairment.

RBD in PSP

The first reported case of RBD in PSP was described in a 70-year old woman who parkinsonism developed one year before the onset of RBD (Pareja et al, 1996). In a series of 15 PSP patients who underwent VPSG, 2 had clinical RBD and 4 had RWA (Arnulf et al, 2005). In another study, 7 of 20 (35%) PSP patients had RBD (Sixel-Döring et al, 2009). These findings argue against RBD as an exclusive feature of the synucleinopathies.

1.2.5. RESTLESS LEGS SYNDROME AND PERIODIC LEG MOVEMENTS IN SLEEP

RLS is characterized by unpleasant urges to move the limbs, precipitated by rest, temporarily relieved by activity, and worse or exclusively present during evening hours (American Academy of Sleep Medicine, 2005). RLS is a very common disorder, affecting approximately 10% of people over the age of 65 years (Rothdach et al, 2000), the prevalence increasing with aging. At least 80% of patients with RLS show PLMS (Montplaisir et al, 1997). PLMS are spontaneous sleep-related movements, frequently involving flexion of the toe, ankle, knee, and hip. Most patients experience repeated flexion of the lower extremities, but some complain of arm movements too. Each movement lasts 0.5 to 10 seconds and occurs at intervals of 5 to 90 seconds, with a remarkable periodicity of approximately 20 to 40 seconds (ICSD, 2005). Several studies have addressed the prevalence of RLS in the PD population: documented rates are between 8% and 20.8% (De Cock et al, 2008). A study of 126 PD patients and 128 healthy age-and sex-matched controls in India found RLS to be present in 10 patients (7.9%) and 1 control (0.8%): PD patients with RLS were older and had a higher

prevalence of depression than those without RLS (Krishnan et al, 2003). Ondo and coworkers evaluated 303 PD patients and found 63 (20.8%) had symptoms of RLS. Neither PD patient demographics nor PD treatments could reliably predict the development of RLS symptoms. PD symptoms preceded RLS symptoms in 54 (68%) of 79 patients with PD/RLS. Compared with patients with idiopathic RLS, patients with PD/RLS were older at RLS onset, were less likely to have a family history of RLS, and had lower serum ferritin levels (Ondo et al, 2002). A study in the Japanese population (Nomura et al, 2006) also found a significantly higher prevalence of RLS in PD patients than in control subjects (12% vs. 2.3%).

A cross-sectional study evaluated and compared sleep disturbances in patients with PD (16 cases), MSA (13 cases), PSP (14 cases) and 12 controls. RLS was frequent (57%) and related to reduced sleep duration and efficiency in PSP. RLS was more frequent in PD and PSP, and in PSP it was associated with reduced sleep efficiency and sleep duration (Gama et al, 2010). Another study evaluated RLS prevalence in 187 consecutive patients with parkinsonian disorders (PD = 134, PSP = 27, MSA = 21, DLB = 5) and in 172 healthy controls. The prevalence of RLS was higher in patients compared to controls (9.6% vs. 2.9%; $p = 0.009$) and was highest in PD (11.9%). RLS was present in only one patient, each with MSA and PSP, and none with DLB (Bhalsing et al, 2013). The SLEEMSA study found that RLS occurred in 28% of patients with MSA, 14% of patients with PD, and 7% of healthy subjects (Moreno-López et al, 2011). The findings of a recent systematic review of case-control VPSG studies in PD (Peeraully et al, 2012) do not support an increased incidence of PLMS in PD patients compared with controls. Sixel-Döring and colleagues found significantly more PLMS in the PD patients with RBD versus the non-RBD PD group, with a mean hourly index of 35 ± 4 versus 22 ± 4 (Sixel-Döring et al, 2011). This finding is mirrored by the significantly increased PLM index in a group of patients with iRBD who eventually developed PD compared to patients with iRBD who remained idiopathic after 6 years of follow-up: 85.2 ±

44.8 vs 35.9 ± 21.1 (Schenck and Boeve, 2011). Motor-behavioural dyscontrol in PD is now shown to extend commonly across wakefulness, REM sleep (RWA/RBD) and non-REM sleep (PLMS), raising the possibility of a common pathogenesis. In MSA, PLMS is a frequent motor sleep disturbance (Iranzo et al, 2009) (Vetrugno et al, 2009): in one study, 88% of 19 MSA patients showed PLMS (Vetrugno et al, 2004). Sixel-Döring and colleagues found that the PLMS and PLMW index were significantly higher in PSP than in PD patients (110.3±79.9 vs 43.7± 47.8; 92.6± 61.0 vs 27.9± 30.8). Overall, PLM indices were >15 in 19/20 PSP patients and 15/20 PD patients (Sixel-Döring et al, 2009).

1.3. AIMS OF THE STUDY

Aim of this study is to describe the possible diagnostic value of sleep disturbances in the differential diagnosis of neurodegenerative diseases characterized by parkinsonian features at onset.

2. PATIENTS AND METHODS

This project is part of the ***BO-ProPark* study** (Bologna-motor and non-motor Prospective study on Parkinsonisms at onset), a prospective longitudinal single centre observational study started in our Department (IRCCS Institute of Neurological Sciences, Bellaria Hospital, Bologna, Italy; Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy) in September 2007. Sixty-five consecutive patients with parkinsonian features and disease duration up to 3 years, evaluated at the Movement Disorders Centre of our Department since January 2008, were consecutively enrolled. Forty-five patients were evaluated twice, at baseline (T0) and 16 months later (T1). Three patients did not complete the study.

2.1. DIAGNOSTIC PROCEDURES

All patients underwent the same evaluation including:

- clinical history and neurological examination
- neuroimaging studies (brain MRI/TC)
- evaluation of autonomic control of the cardiovascular system
- quantification of motor response to standard oral levodopa test
- neuropsychological testing

UPDRS, Beck's Depression Inventory (BDI), Epworth Sleepiness Scale (ESS), PD Sleep Scale (PDSS) 1, criteria for the diagnosis of RLS and RBD questionnaire, were administered. All clinical data useful for diagnosis of PD, MSA, PSP, DLB, CBD and symptomatic forms were described and tabulated with full details in a database developed ad hoc for this study.

Each patient was evaluated twice: the first study was performed at the time of recruitment, and the second study after 16 months. Clinical history was updated, with particular attention to sleep disorders and neurological examination. The appearance of comorbidity, the introduction of new medications for parkinsonism, cognitive and behavioural disturbances were evaluated. At the first evaluation, 10 patients were being treated with dopaminergic drugs (levodopa or dopamine agonists); one patient was being treated with amantadine. Dopaminergic drugs were withdrawn two weeks before sleep evaluation. The diagnosis was made at the second evaluation (T1), according to international diagnostic criteria (Gelb et al, 1999; Emre et al, 2007; Litvan et al, 1996; Gilman et al, 2008; Lang et al, 1994; McKeith et al, 2005) (for international diagnostic criteria see Appendix 1). The patients were diagnosed as:

- PD (Gelb et al, 1999);
- PD plus, which included PD with dementia (PD-D) (Emre et al, 2007), PD with cognitive impairment but not dementia (CIND), in which cognitive functioning falls below normal but who do not meet dementia criteria, and PD with dysautonomia, with prominent neurogenic orthostatic hypotension (OH) defined as a fall in blood pressure of at least 20 mmHg systolic and 10 mmHg diastolic within 3 min in the upright position (Consensus Committee of the American Autonomic Society and the American Academy of Neurology, 1996);
- parkinsonian syndromes (PS), including MSA (Gilman et al, 2008), PSP (Litvan et al, 1996), DLB (McKeith et al, 2005), CBD (Lang et al, 1994) and PS not otherwise specified (when poorly levodopa-responsive parkinsonism occurs, without features suggestive to PSP, MSA, CDB or DLB).

2.2. NIGHT VPSG STUDY

All patients underwent a full night VPSG including EEG (C3-A2, O2-A1, CZ-A1), right and left electro-oculogram (EOG), surface EMG of mentalis, bilateral wrist extensor and tibialis anterior muscles, EKG, microphone, oro-nasal, thoracic and abdominal respirograms, systemic arterial pressure, oxygen saturation and continuous audiovisual acquisition. A sleep laboratory technician monitored each recording. Sleep stages and tonic and phasic components of REM sleep were scored according to the American Academy of Sleep Medicine (AASM) criteria (Iber et al, 2007). According to ASSM and the ICSD (ICSD, 2005) criteria, we evaluated:

- arousal events: the number of arousals and the arousal index (AI) (index: number of events per hour of sleep);
- respiratory events: number of obstructive/central/mixed apnoeas/hypopnoeas and apnoea/hypopnoea index (AHI)
- movement events: PLMS, PLMS index, PLMS/arousal index; excessive fragmentary myoclonus (EFM), hypnic jerks (HJs) and RBD.

PLMS and other simple (EFM, HJs) or complex motor events during sleep (RBD) were checked against the video recording. The tonic and phasic components of REM sleep were scored separately, according to AAMS criteria. Each 30-second epoch was scored as tonic or atonic depending on whether tonic chin EMG activity was present for more or less than 50% of the epoch. In each patient, phasic EMG activity was evaluated in mini-epochs of 3 seconds in all REM sleep periods; a phasic EMG event was defined as any burst of EMG activity lasting 0.1-5.0 seconds with an amplitude exceeding at least 4 times the background EMG activity. Each VPSG was scored by a neurologist blinded to the clinical diagnosis.
This thesis will discuss only VPSG data of the first evaluation.

2.3. STATISTICAL ANALYSIS

We compared PD (group 1: 27 patients) sleep data to PS+PD plus (group 2: 15 patients) sleep data (due to the small sample size, PD plus patients were included in the PS group).

SPSS 12.0 (SPSS, Inc., Chicago, IL) was used for all statistical analyses. Descriptive statistics are given as means ± standard deviation or frequencies (percentages), as applicable. Kruskal Wallis test was used for comparison of quantitative variables among groups. Chi square (X^2) test was used for the between-group comparison to test the association with PLMS disorder, RLS, RBD, EFM, HJs and EDS. A *P*-value $p \leq 0,05$ was considered significant.

3. RESULTS

3.1 PATIENTS' DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

We analysed VPSG data of 42 consecutive patients (15 women; mean age at T0: 61±11 years; range: 37-79 years; mean disease duration at T0: 18±9 months; range: 5-36 months; mean age at onset of motor symptoms: 59±11 years; range: 35-78 years). At the second evaluation (T1) (mean age: 62 ±11 years; range 38-80 years; mean disease duration: 34±9 months; range: 21-52 months), patients were diagnosed according to international diagnostic criteria as:

- 27 PD: 10 women; mean age at onset of motor symptoms: 58±12 years (range: 35-78 years); mean age at T0: 60 ±12 years (range 37-79 years); mean disease duration at T0: 16±8 months (range: 5-36 months); mean age at T1: 61 ±12 years (range 38-80 years); mean disease duration at T1: 32±8 months (range 21-52 months).
- 4 PD plus (2 PD with PD with dysautonomia; 1 PD with CI; 1 PD with dementia): 1 woman; mean age at onset of motor symptoms: 62±9 years (range: 55-76 years); mean age at T0: 63 ±9 years (range 58-77 years); mean disease duration at T0: 15±14 months (range: 7-36 months); mean age at T1: 64 ±9 years (range 59-78 years); mean disease duration at T1: 31±14 months (range 23-52 months).
- 11 parkinsonian syndromes (PS), including PSP (2 patients), MSA (1 patient), CBD (1 patient) and PS not otherwise specified (7 patients): 4 women; mean age at onset of motor symptoms: 60±9 years (range: 40-72 years); mean age at T0: 62 ±10 years (range 41-74 years); mean disease duration at T0: 26±8 months (range: 12-36 months); mean age at T1: 63 ±10 years (range 42-75 years); mean disease duration at T1: 42±8 months (range 28-52 months).

Detailed data on patients' clinical characteristics are summarized in Tables 1 and 2.

Pt ID	GENDER	AGE AT ONSET OF MOTOR SYMPTOMS (years)	DISEASE DURATION T0 (months)	DISEASE DURATION T1 (months)	DIAGNOSIS
1	F	35	18	34	PD
4	M	51	12	28	PD
5	M	76	12	28	PD
6	M	59	24	40	PD
9	F	78	12	28	PD
11	F	56	24	40	PD
13	F	54	36	52	PD
14	F	66	24	40	PD
16	F	61	8	24	PD
17	F	52	36	52	PD
19	M	52	24	40	PD
20	F	40	24	40	PD
24	M	47	5	21	PD
25	M	69	12	28	PD
26	M	63	12	28	PD
27	M	77	7	23	PD
28	M	64	12	28	PD
32	M	72	12	28	PD
33	M	54	18	34	PD
34	F	61	6	22	PD
35	M	68	18	34	PD
36	M	39	24	40	PD
38	M	62	10	26	PD
39	M	74	18	34	PD
41	M	43	9	25	PD
42	M	55	12	28	PD
45	F	48	24	40	PD

Table 1 Demographic characteristics of PD patients. PD: Parkinson disease; M: male; F: female.

Pt ID	GENDER	AGE AT ONSET OF MOTOR SYMPTOMS (years)	DISEASE DURATION T0 (months)	DISEASE DURATION T1 (months)	DIAGNOSIS
10	M	55	36	52	**PDD**
18	M	57	7	23	**PD PLUS 0H**
21	F	76	12	28	**PD PLUS OH**
22	M	61	7	23	**PD PLUS CIND**
2	M	40	12	28	**PS**
3	F	64	36	52	**PS (PSP)**
7	M	67	24	40	**PS**
8	M	63	36	52	**PS**
12	F	58	36	52	**PS (MSA)**
15	M	63	24	40	**PS (PSP)**
31	F	72	24	40	**PS (CBD)**
37	M	62	24	40	**PS**
40	M	68	24	40	**PS**
43	M	52	24	40	**PS**
44	F	49	18	34	**PS**

Table 2 Demographic characteristics of PD plus and PS patients. PD: Parkinson disease; PS: parkinsonian syndrome; PDD: PD with dementia; PSP: progressive supranuclear palsy; MSA: multiple system atrophy; CBD: corticobasal degeneration; OH: orthostatic hypotension; CIND: cognitive impairment not dementia; M: male; F: female.

3.2. SLEEP QUESTIONNAIRE RESULTS AT THE FIRST EVALUATION (T0)

3.2.1. RLS QUESTIONNAIRE

36/42 (24/27 PD; 4/4 PD plus; 8/11 PS) patients completed the RLS questionnaire. RLS symptoms were present in 6/24 PD (25%) and in 6/12 (50%) PS+PD plus patients (2/4 PD plus; 4/8 of PS). There was no significant difference in RLS between the two groups (PD vs PS+PD plus: p=0.13).

3.2.2. ESS

37/42 (24/27 PD; 4/4 PD plus; 9/11 PS) completed the ESS. ESS score was >10 in 3 patients (2/24 PD, 1/9 PS) (p=0.80). No patients referred sleep attacks, even after dopaminergic treatment.

3.3.3. PDSS-1

38/42 (25/27 PD; 4/4 PD plus; 9/11 PS) patients completed PDSS-1. Total PDSS-1 score was 123.3 ± 17.5 in PD patients and 115.4 ± 25.7 in PS+PD plus patients.

For detailed data see Tables 3 and 4.

Pt ID	QUESTIONNAIRE POSITIVE FOR RLS	ESS SCORE	PDSS-1 SCORE	DIAGNOSIS
1	**YES**	8	85.8	**PD**
4	NO	**11**	94.3	**PD**
5	NO	2	119.2	**PD**
6	NO	3	131.8	**PD**
9	NO	1	133.9	**PD**
11	**YES**	7	128.5	**PD**
13	NO	2	128.1	**PD**
14	NO	2	124.4	**PD**
16	NO	3	146.6	**PD**
17	NO	3	126	**PD**
19	NO	2	117.1	**PD**
20	**YES**	2	135.9	**PD**
24	NO	7	134.3	**PD**
25	**YES**	2	131.5	**PD**
26	NO	-	121	**PD**
27	NO	9	119.1	**PD**
28	NO	8	123.2	**PD**
32	-	2	126.4	**PD**
33	NO	10	130.3	**PD**
34	NO	8	128	**PD**
35	**YES**	10	134	**PD**
36	NO	10	119.2	**PD**
38	**YES**	**15**	67.1	**PD**
39	NO	2	136.5	**PD**
41	-	-	-	**PD**
42	NO	8	142.5	**PD**
45	-	-	-	**PD**

Table 3. Sleep questionnaire results of PD patients. RLS: restless legs syndrome; ESS: Epworth sleepiness scale; PDSS-1: PD Sleep scale.

Pt ID	QUESTIONNAIRE POSITIVE FOR RLS	ESS SCORE	PDSS SCORE	DIAGNOSIS
10	**YES**	9	120.4	**PDD**
18	NO	10	122.1	**PD PLUS 0H**
21	**YES**	7	79.7	**PD PLUS OH**
22	NO	3	130	**PD PLUS CIND**
2	NO	6	134.6	**PS**
3	**YES**	**16**	49.9	**PS (PSP)**
7	NO	3	131.7	**PS**
8	NO	9	130.8	**PS**
12	**YES**	6	128.5	**PS (MSA)**
15	NO	1	133.4	**PS (PSP)**
31	NO	2	91.4	**PS (CBD)**
37	NC	1O	127.1	**PS**
40	**YES**	5	120.7	**PS**
43	NC	-	-	**PS**
44	NC	-	-	**PS**

Table 4. Sleep questionnaire results of PD plus and PS patients. RLS: restless legs syndrome; ESS: Epworth sleepiness scale; PDSS-1: PD Sleep scale.

3.3. VPSG RESULT AT THE FIRST EVALUATION (T0)

3.3.1. SLEEP PARAMETERS

Sleep efficiency (SE) was reduced in all patients, with a mean value of 61±16% of total sleep time (TST) (normal value >85%). No difference in SE was seen between the two groups (mean value PD patients: 65.3±10.1% of TST; mean value PS+PD plus patient: 54.7±22.3% of TST) (p=0.112). Both groups showed a reduced TST (PD TST: 258 ± 49 min vs PS+PD plus TST: 213 ± 90 min; p=0.181). All sleep stages were represented (Stage 1: 5.5 ± 3.1% in

PD versus 8.1 ± 11.3% in PS+PD plus patients; p=0.990; Stage 2: 44.1 ± 12.3% in PD versus 48.4 ± 13.3 % in PS+PD plus patients; p= 0.423; Stage 3: 31.5 ± 9.9% in PD versus 26.7 ± 11.5% in PS+PD plus patients; p= 0.487; Stage REM: 18.9 ± 8.0% in PD versus 16.8 ± 9.7% in PS+PD plus patients; p=0.646). There was no significant difference in TST, sleep stage duration or percentages and sleep latency or between the two groups.

Wake after sleep onset (WASO) was higher in PS+PD plus patients (43.6 ± 22.2%) (158.0 ± 72.5 min) than in PD patients (30.7 ± 9.8%) (113.7 ± 36.5 min) (p=0.047) (p=0.032).

For detailed results see Tables 5, 6 and 7.

SLEEP PARAMETERS	**PD** **n=27**	**PS + PD PLUS** **n= 15**	***p* values**
SLEEP EFFICIENCY (% OF TST)	65.3±10.1	54.7±22.3	0.112
TST (min)	258 ± 49	213 ± 90	0.181
SLEEP LATENCY (min)	23±20	14±9	0.172
STAGE 1 (% OF TST)	5.5 ± 3.1	8.1 ± 11.3	0.990
STAGE 2 (% OF TST)	44.1 ± 12.3	48.4± 13.3	0.423
STAGE 3 (% OF TST)	31.5 ± 9.9	26.7 ± 11.5	0.487
STAGE REM (% OF TST)	18.9 ± 8.0	16.8 ± 9.7	0.646
WASO (% OF TST)	30.7 ± 9.8	43.6 ± 22.2	**0.047**
STAGE 1 % (min)	14.1 ± 7.9	11.2 ± 6.9	0.253
STAGE 2 (min)	114 ± 39	98 ± 36	0.243
STAGE 3 (min)	80 ± 27	62 ± 36	0.121
STAGE REM (min)	49.7± 24.6	42 ± 32	0.408
WASO (min)	113.7 ± 36.5	8.1 ± 11.3	**0.032**

Table 5. Sleep parameters of PD patients and PS+ PD plus patients TST: total sleep time; WASO: wake after sleep onset; SE: sleep efficiency.

Pt ID	TST (min)	STAGE 1 (%)	STAGE 2 (%)	STAGE 3 (%)	STAGE REM (%)	WASO (%)	SE (%)	SLEEP LATENCY (min)	REM LATENCY (min)	DIAGNOSIS
1	266.0	3.9	47.0	34.6	14.5	25.2	66.8	43.0	94.0	PD
4	315.5	8.4	47.1	20.0	24.6	18.8	79.6	8.0	77.0	PD
5	237.5	5.3	20.4	41.7	32.6	34.9	61.0	24.5	53.5	PD
6	238.5	3.1	43.6	28.1	25.2	37.1	58.5	28.5	66.5	PD
9	203.5	7.6	59.5	29.2	3.7	38.2	60.3	8.5	163.5	PD
11	280.5	3.2	44.2	28.0	24.6	26.7	70.9	13.0	82.0	PD
13	330.5	2.6	48.0	22.5	26.9	14.2	78.7	35.0	104.0	PD
14	248.0	3.8	65.3	24.6	6.3	30.0	68.5	7.5	251.0	PD
16	173.0	1.4	35.0	54.3	9.2	49.6	50.4	0.5	107.0	PD
17	304.0	2.6	49.8	28.3	19.2	16.6	77.3	29.0	131.5	PD
19	224.5	3.3	60.8	17.1	18.7	26.8	59.5	71.0	186.5	PD
20	334.0	6.6	62.7	16.8	13.9	26.5	72.0	21.0	220.0	PD
24	261.0	3.1	47.7	39.5	9.8	32.9	66.9	2.5	78.0	PD
25	170.0	5.0	31.2	30.0	33.8	40.1	45.3	91.5	109.0	PD
26	224.5	5.6	45.4	32.7	16.3	42.0	55.5	19.0	66.0	PD
27	282.5	4.3	48.5	28.3	18.9	22.8	75.1	10.0	45.5	PD
28	228.5	7.7	60.0	26.3	6.1	26.9	63.8	47.0	152.0	PD
32	264.0	9.3	59.1	15.0	16.7	39.4	60.6	12.0	223.5	PD
33	240.5	3.3	34.1	41.6	21.0	39.3	58.9	13.5	48.5	PD
34	355.5	3.0	27.4	38.1	31.5	11.5	86.4	11.5	39.0	PD
35	229.5	2.6	25.3	44.4	27.7	38.1	57.7	28.5	242.0	PD
36	216.0	13.7	37.3	31.5	17.6	39.7	58.6	11.5	192.5	PD
38	211.0	9.2	50.9	27.0	12.8	44.1	52.6	25.0	280.0	PD
39	286.0	10.1	37.1	36.4	16.4	26.9	70.9	14.0	60.0	PD
41	227.5	9.7	39.8	31.9	18.7	37.7	58.5	25.5	42.0	PD
42	45.0	46.7	43.3	10.0	0.0	83.7	15.0	24.5	276.5	PD
45	266.0	3.9	47.0	34.6	14.5	25.2	66.8	43.0	94.0	PD

Table 6. PD patients' sleep parameters. TST: total sleep time; WASO: wake after sleep onset; SE: sleep efficiency.

Pt ID	TST (min)	STAGE 1 (%)	STAGE 2 (%)	STAGE 3 (%)	STAGE REM (%)	WASO (%)	SE (%)	SLEEP LATENCY (min)	REM LATENCY (min)	DIAGNOSIS
10	298.0	3.7	51.2	29.7	15.4	25.0	74.5	2.5	146.0	PDD
18	262.5	6.9	50.7	23.0	19.4	28.0	70.1	10.0	64.5	PD PLUS 0H
21	212.0	2.1	41.3	36.1	20.5	41.6	56.3	15.5	40.5	PD PLUS OH
22	130.5	7.7	71.6	13.4	7.3	66.8	31.0	29.0	359.0	PD PLUS CIND
2	345.5	2.2	37.3	36.9	23.6	4.8	94.7	2.0	72.5	PS
3	259.5	10.4	49.1	13.5	27.0	40.4	57.2	18.5	188.5	PS (PSP)
7	304.0	1.8	36.8	26.7	34.7	20.5	77.4	10.5	76.5	PS
8	240.0	2.9	47.3	33.1	16.7	35.6	59.7	29.5	112.0	PS
12	78.0	12.8	75.6	2.6	9.0	78.8	20.6	12.0	59.5	PS (MSA)
15	160.0	3.8	47.5	38.1	10.6	52.8	47.1	0.5	13.5	PS (PSP)
31	174.0	0.3	67.2	31.6	0.9	53.3	44.7	18.0	257.5	PS (CBD)
37	273.5	5.5	35.3	34.6	24.7	33.5	64.7	13.0	88.5	PS
40	124.0	9.7	32.7	38.7	19.0	61.9	36.6	15.0	65.5	PS
43	284.0	4.8	39.4	32.6	23.2	28.6	71.5	4.5	32.5	PS
44	287.0	2.8	25.4	52.3	19.5	26.3	70.0	22.0	155.0	PS

Table 7. PD plus and PS patients' sleep parameters. TST: total sleep time; WASO: wake after sleep onset; SE: sleep efficiency.

3.3.2. REM FEATURES

REM latency was increased in all patients (124.9 ± 83.8 min): no difference was seen between PD (123.0 ± 73.0 min) and PS+PD plus patients (124.0 ± 102 min) (p=0.627). The mean percentage of epochs with enhanced tonic muscle EMG activity during REM sleep was higher in PD plus and PS (14 ± 33% of REM sleep epochs; range 0-100) than in PD patients (4 ± 15% of REM sleep epochs; range 0-78) (p=0.034). No difference in phasic muscle EMG activity during REM sleep was seen between the two groups (PD: 8 ± 17% of REM sleep epochs, range 0-72; PS+PD plus 12 ± 14% of REM sleep epochs, range 0-38) (p=0.335).

RBD episodes were recorded in 7 patients (2/27 PD; 3/4 PD plus; 2/11 PS). Ten (4/27 PD, 3/4

PD plus, 3/11 PS) patients had a positive questionnaire for RBD: at least one RBD episode was recorded in 7/10 (2 PD, 3 PD plus, 2 PS). No RBD episodes were recorded in 1 PS patient (patient 3) with a positive questionnaire for RBD, but VPSG documented an excessive phasic muscle activity (35.7% of epochs) during REM sleep. In 2 PD patients (patient 26 and patient 39) with a positive questionnaire for RBD, VPSG documented a normal atonia during REM sleep and no RBD episodes were recorded. According to AASM criteria, the diagnosis of RBD was made in 2/27 (7.4%) PD patients and 6/15 (40%) PS and PD plus patients (p=0.01). In particular, in group 2 a diagnosis of RBD was made in 3/4 (75%) of PD plus patients and 3/11 (27%) of PS patients (1 PSP, 1 MSA, 1 PS not otherwise specified). Detailed data on patients' REM sleep features are summarized in Tables 8, 9 and 10.

REM PARAMETERS	**PD** **n=27**	**PS + PD PLUS** **n= 15**	***p* values**
REM LATENCY (min)	123±73	124±102	0.627
TONIC MUSCLE EMG ACTIVITY (% OF REM EPOCHS)	4 ± 15	14± 33	**0.034**
PHASIC MUSCLE EMG ACTIVITY (% OF REM EPOCHS)	8±17	12±14	0.335

Table 8. REM sleep features of PD patients and PS+ PD plus patients.

Pt ID	STAGE REM (%)	PHASIC ACTIVITY (% of epochs)	TONIC ACTIVITY (% of epochs)	RBD DURING VPSG	QUESTIONNAIRE POSITIVE FOR RBD	DIAGNOSIS
1	14.5	0.0	0.0	NO	NO	**PD**
4	24.6	1.3	9.0	NO	NO	**PD**
5	32.6	0.0	0.0	NO	NO	**PD**
6	25.2	0.0	0.0	NO	NO	**PD**
9	3.7	13.3	0.0	NO	NO	**PD**
11	24.6	0.0	0.0	NO	NO	**PD**
13	26.9	7.9	1.7	NO	NO	**PD**
14	6.3	0.0	0.0	NO	NO	**PD**
16	9.2	0.0	0.0	NO	NO	**PD**
17	19.2	0.0	0.0	NO	NO	**PD**
19	18.7	16.7	0.0	NO	NO	**PD**
20	13.9	0.0	0.0	NO	NO	**PD**
24	9.8	0.0	0.0	NO	NO	**PD**
25	33.8	3.5	0.0	NO	NO	**PD**
26	16.3	1.4	0.0	NO	**YES**	**PD**
27	18.9	4.7	0.0	NO	NO	**PD**
28	6.1	10.7	0.0	NO	NO	**PD**
32	16.7	11.4	0.0	NO	NO	**PD**
33	21.0	13.9	0.0	NO	NO	**PD**
34	31.5	0.4	0.0	NO	NO	**PD**
35	27.7	**52.8**	**13.4**	**YES**	**YES**	**PD**
36	17.6	10.5	0.0	NO	NO	**PD**
38	12.8	**72.2**	**77.8**	**YES**	**YES**	**PD**
39	16.4	0.0	0.0	NO	**YES**	**PD**
41	18.7	5.9	0.0	NO	NO	**PD**
42	0.0	0.0	0.0	NO	NO	**PD**
45	14.5	0.0	0.0	NO	NO	**PD**

Table 9. PD patients' REM sleep features.

Pt ID	STAGE REM (%)	PHASIC ACTIVITY (% of epochs)	TONIC ACTIVITY (% of epochs)	RBD DURING VPSG	QUESTIONNAIRE POSITIVE FOR RBD	DIAGNOSIS
10	15.4	**26.1**	1.1	**YES**	**YES**	**PDD**
18	19.4	**18.6**	0.0	**YES**	**YES**	**PD PLUS 0H**
21	20.5	**17.2**	**100.0**	**YES**	**YES**	**PD PLUS OH**
22	7.3	5.3	0.0	NO	NO	**PD PLUS CIND**
2	23.6	0.0	0.6	NO	NO	**PS**
3	27.0	**35.7**	0.7	NO	**YES**	**PS(PSP)**
7	34.7	1.4	0.0	NO	NO	**PS**
8	16.7	**37.5**	**92.5**	**YES**	**YES**	**PS**
12	9.0	**14.3**	**14.3**	**YES**	**YES**	**PS (MSA)**
15	10.6	0.0	0.0	NO	NO	**PS (PSP)**
31	0.9	0.0	0.0	NO	NO	**PS (CBD)**
37	24.7	0.0	0.0	NO	NO	**PS**
40	19.0	21.3	6.4	NO	NO	**PS**
43	23.2	0.0	0.0	NO	NO	**PS**
44	19.5	0.0	0.0	NO	NO	**PS**

Table 10. PD plus and PS patients' REM sleep features.

3.3.3. AROUSAL INDEX

No difference in arousal index (AI) was seen between groups (AI in PD: 13.4 ± 7, range 3.1-35.9 versus AI in PS+ PD plus: 11.5 ± 4.9, range 3.9-21.3) (p=0.572). For detailed results see Table 11.

3.3.4. PLMS DISORDER AND OTHER SIMPLE MOTOR EVENTS DURING SLEEP

No difference in PLMS index (PD: 40.6 ± 53.8 versus PS+PD plus: 37.2 ± 47.5; p=0.875), PLMS NREM sleep index (PD: 41.4 ± 53.6 versus PS+PD plus: 36.9± 48; p=0.885), PLMS

REM sleep index (PD: 37.1 ± 63.6 versus PS+PD plus: 36 ± 51.8; p = 0.812), PLMS/arousal index (PD: 3.9 ± 4.7 versus PS+PD plus: 1.9 ± 1.8; p = 0.492), PLMS/arousal NREM index (PD: 4.5 ± 5.7 versus PS+PD plus: 2.0 ± 2.0; p = 0.321) or PLMS/arousal REM index (PD: 1.3 ± 3.1 versus PS+PD plus: 1.1 ± 2.1, p = 0.913) was seen between groups.

The PLMS index was ≥ 15 in 16/27 (59%) PD patients and in 10/15 (66.6%) PS+PD plus patients. HJs were more frequent in PS+PD plus patients (5/15 patients, 33.3%) than in PD patients (2/27 patients, 7.4%) (p=0.03).

No difference was seen between groups in EFM recorded in 3/27 (11.1%) PD patients and 5/15 (33.3) PS + PD plus patients (p=0.06). For detailed results see Table 11.

3.3.5. RESPIRATORY EVENTS DURING SLEEP

The AHI was higher in PS + PD plus patients (AHI: 9 ± 13; range 0-35) than in PD patients (AHI: 5 ± 14; range 0-62)(p = 0.018). VPSG diagnosis of OSAS (AHI ≥ 10) was made in 4 patients: 1/27 PD (3.7%) (patient 38: AHI = 30.9) and 3/15 PS patients (20%) (patient 8: AHI=16.25; patient 15: AHI=27.75; patient 37: AHI: 34.6) (p=0.08). Stridor was not detected in any patients. For detailed results see Table 11.

	PD n=27	PS + PD PLUS n= 15	*p* values
AROUSAL INDEX	13.4±7	11.5±4.9	0.572
PLMS INDEX	40.6 ± 53.8	37.2 ± 47.5	0.875
PLMS NREM INDEX	41.4±53.6	36.9±48	0.885
PLMS REM INDEX	37.1 ± 63.6	36 ± 51.8	0.812
PLMS/AROUSAL INDEX	3.9 ± 4.7	1.9 ± 1.8	0.492
PLMS/AROUSAL NREM INDEX	4.5 ± 5.7	2± 2	0.321
PLMS/AROUSAL REM INDEX	1.3± 3.1	1.1 ± 3.1	0.913
APNOEA/HYPOPNOEA INDEX	5± 14	9 ± 13	**0.018**

Table 11. Arousal, motor and respiratory events of PD patients and PS+ PD plus patient

4. DISCUSSION

We compared the VPSG features of 27 consecutive patients with PD and 15 consecutive patients with atypical parkinsonism (PS and PD plus patients) at disease onset. Our aim was to evaluate the possible diagnostic value of sleep disturbances in the differential diagnosis of neurodegenerative diseases characterized by parkinsonian features at onset.

Our findings show a severely reduced SE and TST in all patients, with a significant increase in WASO in patients with atypical parkinsonisms (PS and PD plus) than in PD patients. No significant differences between groups of patients were detected in other sleep parameters.

Analysing REM sleep features, we found that the mean percentage of epochs with enhanced tonic muscle EMG activity during REM sleep was higher in PD plus and PS than in PD. No difference in phasic muscle EMG activity during REM sleep was seen between the two groups. Moreover, RBD was more frequent in PD plus and PS than in PD patients: a diagnosis of RBD (according to AASM criteria) was made in 7.4% of PD patients and 40% of PS and PD plus patients (75% of PD plus patients and 27% of PS patients). These results suggest that RBD is rarely present in early untreated PD, whereas it is more common in PD associated with dysautonomia or CIND/dementia, also in the early stage of disease. These data seem to conflict with literature reports of a prevalence of RBD in PD patients ranging between 46% and 58% (Iranzo et al, 2009), but most of these studies involved patients in different disease stages who had already been treated with dopaminergic drugs. Few VPSG studies involved newly diagnosed dopaminergic treatment-naïve PD patients: one study in untreated PD patients reported a RBD prevalence of 30%, not associated with CI (Plomhause et al, 2013), whereas another study found RBD rarely present in early untreated PD (only in 1/20 PD patients) (Buskova et al, 2011). The DeNoPa cohort (Mollenhauer et al, 2013) made a diagnosis of RBD in 40/159 (25%) newly diagnosed drug naïve PD patients (disease

duration < 2 years, range 9-24 months): these patients underwent neuropsychological testing of executive functions, attention and speech, verbal fluency, memory and visuospatial function, but no autonomic tests were performed to evaluate possible OH. Moreover, no longitudinal patient data are available in the DeNoPa cohort, and patients with atypical PD at an early stage of their illness may have been included.

Our results indicate that the presence of RBD at disease onset in PD patients would suggest the possible future appearance of cognitive or dysautonomic symptoms, as seen in PD plus patients, in agreement with literature data confirming that RBD in PD patients is associated with dementia and OH (Postuma et al, 2008) (Postuma et al, 2012) (Romenets et al, 2012). These results suggest that RBD may be a marker of a relatively diffuse and complex subtype of PD. Pathological changes in the brainstem structures modulating REM sleep, responsible for RBD and RWA, seem to be present earlier in PD plus and PS patients than in PD patients. HJs, brief and sudden trunk and limb jerks during NREM sleep, similar to but less complex than those occurring in the same patients during REM sleep, were observed in PD plus and PS patients more frequently than in PD patients. The same observation was reported by other authors (Iranzo et al, 2009) (Vetrugno et al, 2009) in patients with MSA, suggesting that these non-REM sleep motor abnormalities in MSA patients are indicators of dissociated states of sleep, in which components of one state intrude into another. Another explanation for these results might be that motor-behavioural dyscontrol in atypical parkinsonisms tends to extend across wakefulness, REM sleep (RWA/RBD) and NREM sleep (HJs), more frequently and/or earlier than in PD.

Only 1/27 (3.7%) PD patients have OSAS versus 20% (3/15) of PS+PD plus patients whose AHI is higher than that of PD patients. Sleep apnoea does not seem to be clinically relevant in PD patients, while patients with atypical parkinsonisms (PS and PD plus) are a greater risk of developing disordered breathing events during sleep. These results are probably related to an

early and more marked damage of brain areas involved in the automatic control of respiration (Benarroch, 2003).

RLS symptoms were present in 6/24 PD (25%) and in 6/12 (50%) PS+PD plus patients, substantially in agreement with literature data.

EDS is not clinically relevant in our sample of patients, with ESS scores >10 in only three cases (2/24 PD, 1/9 PS). These frequencies are lower than those obtained in other studies, that included patients in different disease stages and often treated with dopamine agonists, whereas our patients were drug naïve and with recent onset of disease. These factors may explain the lower frequency of EDS in our group of patients.

The main strength of this study is its focus on consecutively analysing newly diagnosed parkinsonian patients with a short disease duration prior to dopaminergic treatment. Moreover, the longitudinal follow-up of our cohort with serial VPSG provided opportunities to clarify the evolution of sleep disorders with disease progression in neurodegenerative diseases characterized by parkinsonian features. Another major strength of the study is that the diagnosis was not only clinical, but also instrumental: all patients underwent autonomic and neuropsychological tests, so the diagnosis of OH and dementia are well documented.

We are aware of several limitations of our study, including:

1) The lack of an age and gender matched control group, due to the difficulty in finding appropriate controls (healthy individuals, matched for age and gender). However, our aim was not to differentiate patients from controls, but to differentiate different groups of patients to disclose features useful for differential diagnosis;

2) The lack of dual-night VPSG controlling the first-night effect;

3) The small sample of patients, especially PS and PD plus patients.

5. CONCLUSIONS

Our data suggest that REM sleep motor control (RWA/RBD) is more frequently impaired at disease onset in patients with PS and PD plus compared to PD patients. The presence of RBD or an enhanced tonic muscle EMG activity in a patient with recent onset parkinsonian features should suggest a diagnosis of atypical parkinsonism, rather than PD. More data are needed to establish the diagnostic value of these features in the differential diagnosis of parkinsonisms. The evaluation of sleep disorders, with an in-depth clinical interview followed by VPSG, may be a useful tool in the differential diagnosis of parkinsonism at onset.

APPENDIX 1

DIAGNOSTIC CRITERIA FOR PD (Gelb et al, 1999)

GROUP A: **Features characteristic of PD**

- Resting tremor
- Bradykinesia
- Rigidity
- Asymmetric onset

GROUP B: **Features suggestive of alternative diagnoses**

- Features unusual early in the clinical course: prominent postural instability in the first 3 years after symptom onset;
- freezing phenomena in the first 3 years; hallucinations unrelated to medications in the first 3 years; dementia preceding motor symptoms or in the first year;
- supranuclear gaze palsy or slowing of vertical saccades;
- severe, symptomatic dysautonomia unrelated to medications;
- documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months).

POSSIBLE PD

At least 2 of the 4 features in group A are present;
at least 1 of these is tremor or bradykinesia.
And either:
- none of the features in group B is present or symptoms have been present for less than 3 years, and none of the features in Group B is present to date
and either:
- substantial and sustained response to levodopa or a dopamine agonist has been documented or patient has not had an adequate trial of levodopa or dopamine agonist.

PROBABLE PD

At lest 3 of the 4 features in group A are present and none of the features in group B is present (note: symptom duration of at least 3 years is needed to meet this requirement) and substantial and sustained response to levodopa or a dopamine agonist has been documented.

DEFINITE PD

All criteria for POSSIBLE Parkinson disease are met and histopathological confirmation of the diagnosis is obtained at autopsy.

DIAGNOSTIC CRITERIA FOR PDD (Emre et al, 2007)

I. Core features

Diagnosis of PD disease according to Queen Square Brain Bank criteria

A dementia syndrome with insidious onset and slow progression, developing within the context of established PD and diagnosed by history, clinical, and mental examination, defined as: Impairment in more than one cognitive domain representing a decline from premorbid level.

Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms.

II. Associated clinical features

Cognitive features: **Attention: Impaired**. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day. **Executive functions: Impaired**. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia). **Visuospatial functions: Impaired.** Impairment in tasks requiring visual-spatial orientation, perception, or construction. **Memory: Impaired**. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall. **Language: Core functions largely preserved**. Word finding difficulties and impaired comprehension of complex sentences may be present.

Behavioural features: **Apathy: decreased spontaneity**; loss of motivation, interest, and effortful behaviour **Changes in personality and mood** including depressive features and anxiety. **Hallucinations**: mostly visual, usually complex, formed visions of people, animals or objects. **Delusions**: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions. **Excessive daytime sleepiness**.

III. Features which do not exclude PD-D, but make the diagnosis uncertain

Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging.

Time interval between the development of motor and cognitive symptoms not known.

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D

- Cognitive and behavioural symptoms appearing solely in the context of other conditions such as: Acute confusion due to a. Systemic diseases or abnormalities b. Drug intoxication Major Depression according to DSM IV
- Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Probable PD-D

A. Core features: Both must be present B. Associated clinical features:

• Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuospatial functions, and impaired free recall memory which usually improves with cueing)

• The presence of at least one behavioural symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioural symptoms, however, does not exclude the diagnosis

C. None of the group III features present

D. None of the group IV features present

Possible PD-D

A. Core features: Both must be present B. Associated clinical features:

• Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention

• Behavioural symptoms may or may not be present OR

C. One or more of the group III features present

D. None of the group IV features present

DIAGNOSTIC CRITERIA FOR MSA (Gilman et al, 2008)

PROBABLE MSA

A sporadic, progressive, adult (>30 y)–onset disease characterized by
- autonomic failure involving urinary incontinence or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic *and*
- poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) *or*
- a cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

POSSIBLE MSA

A sporadic, progressive, adult (>30 y)–onset disease characterized by
- parkinsonism *or*
- a cerebellar syndrome *and*
- at least one feature suggesting autonomic dysfunction *and*
- at least one of the additional features

Additional features of POSSIBLE MSA

Possible MSA-P or MSA-C

- Babinski sign with hyperreflexia
- Stridor

Possible MSA-P

- Rapidly progressive parkinsonism
- Poor response to levodopa
- Postural instability within 3 years of motor onset
- Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
- Dysphagia within 5 years of motor onset
- Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
- Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum

Possible MSA-C

- Parkinsonism (bradykinesia and rigidity)
- Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
- Hypometabolism on FDG-PET in putamen
- Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

DIAGNOSTIC CRITERIA FOR PSP (Litvan et al, 1996)

POSSIBLE PSP

Gradually progressive disorder with onset at age 40 or later.
Either vertical supranuclear palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year of onset.
No evidence of other diseases that can explain the clinical features, as indicated by mandatory exclusion criteria.

PROBABLE PSP

Gradually progressive disorder with onset at age 40 or later.
Vertical supranuclear palsy *and* prominent postural instability, with falls in the first year of disease.
No evidence of other diseases that can explain the clinical features, as indicated by mandatory exclusion criteria.

Supportive criteria

- Symmetric akinesia or rigidity, proximal more than distal
- Abnormal neck posture, especially retrocollis
- Poor or absent response of parkinsonism to levodopa therapy
- Early dysphagia and dysarthria
- Early cognitive impairment with at least 2 of the following: apathy, abstract thought impairment, decreased verbal fluency, imitation behaviour, or frontal release signs.

Mandatory exclusion criteria

- Recent history of encephalitis
- Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy.
- Hallucination or delusions unrelated to dopaminergic therapy
- Cortical dementia of Alzheimer's type
- Prominent, early cerebellar symptoms or prominent, early unexplained dysautonomia
- Severe, asymmetric parkinsonian signs
- Neuroradiologic evidence of relevant structural abnormality
- Whipple disease's, confirmed by polymerase chain reaction, if indicated

DIAGNOSTIC CRITERIA FOR CBD (Lang et al, 1994)

Inclusion criteria

Rigidity plus one cortical sign (apraxia, cortical sensory loss, or alien limb) *or* asymmetric rigidity, dystonia and focal reflex myoclonus.

Exclusion criteria

Early dementia
Early vertical gaze palsy
Rest tremor
Severe autonomic disturbance
Sustained response to levodopa
Lesions on imaging studies indicate another pathological process

DIAGNOSTIC CRITERIA FOR DLB (McKeith et al, 2008)

Central features (essential for diagnosis of POSSIBLE and PROBABLE DLB)

- Dementia, defined as progressive mental decline serious enough to interfere with normal daily activities.
- Prominent or persistent memory impairment may not necessarily occur in the early stage but is usually evident with progression.
- Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.

Core features (two core features are sufficient for diagnosis of PROBABLE DLB, one for POSSIBLE DLB)

- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations typically well-formed and detailed
- Spontaneous features of parkinsonism

Suggestive symptoms (if one or more of these is present in the presence of one or more core features, a diagnosis of PROBABLE DLB can be made. In the absence of any core features, one or more suggestive symptoms is sufficient for a diagnosis of POSSIBLE DLB)

- RBD
- Severe neuroleptic sensitivity
- Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging.

Supportive symptoms (commonly present but not proven to have diagnostic specificity)

- Repeated falls and syncope
- Transient, unexplained loss of consciousness
- Severe autonomic dysfunction
- Hallucinations in other modalities
- Delusions
- Depression
- Relative preservation of medial temporal lobe structures on CT/MRI scan
- Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
- Abnormal (low uptake) MIBG myocardial scintigraphy
- Prominent slow wave activity on EEG

DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term PD dementia (PDD) should be used to describe dementia that occurs in the context of well-established PD.

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