Parkinson's disease and periodic limb movement in sleep

Doença de Parkinson e movimentos periódicos dos membros durante o sono

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ABSTRACT

Parkinson's disease is a neurodegenerative disease understood as a complex syndrome with motor and non-motor symptoms, including sleep-related conditions, such as periodic limb movements in sleep (PLMS). This paper presents issues regarding Parkinson's disease, motor and non-motor symptoms, sleep physiology, and PLMS. In conclusion, both conditions seem to be correlated through impairment of the dopaminergic system.

Keywords: Parkinson's disease, nonmotor symptoms, sleep, periodic limb movement.

RESUMO

A doença de Parkinson é uma doença neurodegenerativa entendida como uma síndrome complexa com sintomas motores e não motores, incluindo condições relacionadas ao sono, como movimentos periódicos dos membros durante o sono (MPMS). Este artigo apresenta questões relacionadas à doença de Parkinson, sintomas motores e não motores, fisiologia do sono e MPMS. Em conclusão, ambas as condições parecem estar correlacionadas por comprometimento do sistema dopaminérgico.

Palavras-chave: Doença de Parkinson, sintomas não motores, sono, movimento periódico dos membros.

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INTRODUCTION

Patients with Parkinson's disease (PD) have a plethora of motor and non-motor symptoms. These last include periodic limb movements in sleep (PLMS) that are repetitive movements, most typically in the lower limbs. However, periodic limb movement disorder (PLMD) happens when patients with PLMS have associated clinical sleep disturbance or a complaint of daytime fatigue. Both PD and PLMD may respond to dopamine agonists. This association raises many issues regarding shared pathophysiology, as will be unfolded [1] .

PARKINSON'S DISEASE

PD is a progressive neurodegenerative disease capable of causing various motor and non-motor symptoms which usually develop slowly, mainly affecting people over 65 years of age, with a predominance of males over females.

The diagnosis of PD depends on the motor symptoms caused by clinical effects of dopamine deficiency, so most patients are usually diagnosed when the disease progression is advanced and about 50% of dopaminergic neurons in the substantia nigra (SN) are already absent, with treatment start delay [2] .

Clinical effects of dopamine deficiency include bradykinesia, rigidity, and tremor at rest, usually manifesting asymmetrically, besides postural instability [2]. Non- motor symptoms include mood disorders, autonomic dysfunctions, fatigue, pain, cognitive changes, gastrointestinal dysfunctions, perceptual distortions, attention deficit and sleep disorders, which is one of the commonly reported non-motor markers in patients with PD, as well as in other neurodegenerative disorders (atypical parkinsonian syndromes) 3 . Many of these symptoms are included in Figure 1.

Olfactory loss, REM sleep behavior disorder, constipation and subtle motor parkinsonism are among the strongest predictors to clinical PD presentation, and the period lag between the onset of these symptoms and the onset of PD varies from 5 years, for motor symptoms, to over 20 years, for autonomic symptoms [2] .

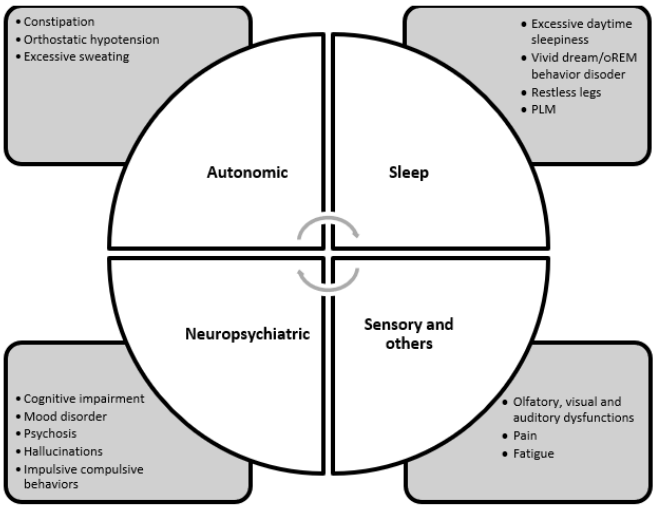

Figure 1. Parkinson disorders non-motor symptoms[2].

The etiology of PD is poorly understood, but the interaction between genetic factors and environmental risk factors seems to contribute to its neuropathogenesis. Probably multiple etiologies contribute jointly to the disease's development.

Neuroimaging testing can provide diagnosis confirmation and prevent possible misdiagnosis due to PD's overlapping symptoms with other neurodegenerative disorders, and DaTscan enables assessment of affected nigrostriatal dopaminergic neurons terminals for PD investigation. PD patients tend to have *striatum* (caudate and putamen) minor signal on DaTscan related to dopamine deficiency [4].

The predominant symptoms of PD are caused by the loss of dopaminergic neurons in the substantia nigra, and the nigrostriatal degeneration is a result of the depletion and final loss of the neurotransmitter dopamine at the synaptic terminals of striated neurons. As a result, replacement therapy is required. Other functional brain networks are also usually affected, such as those of mood, behavior, and cognition. Also, PD is linked to the abnormal presence of Lewy bodies, insoluble fibrillar aggregates formed by a protein present in the human brain called alpha-synuclein[4].

As presented in Figure 2, based on Braak et al. 2003 apud Keo et al. [5] the PD degenerative process would begin in non-dopaminergic structures that ascends caudo-rostrally from the lower brainstem and forebrain, into the cerebral cortex. Six PD Braak´s stages are presented sequentially depending on the accumulated Lewy bodies during disease progression. This staging model implicates environmental factors, such as toxins or inflammatory agents, which can trigger the aggregation of α-synuclein, the Lewy body, that come into contact with olfactory and/or enteric neurons. The aggregated α-synuclein spreads toward the central nervous system via the olfactory bulb and the vagus nerve, but probably genetic factors are likely to contribute to PD.

It is beyond the scope of this article to discuss the mechanisms of formation and spread of the misfolded prion-like alpha-synuclein through the brain and synaptically coupled neuroanatomical tracts. However, this would justify much earlier symptomatology when compared to the classical one. It is illustrated in six different stages. The former are marked by non-motor symptoms, then motor symptoms often displayed around the mid-stage state, and cognitive symptoms arising later.

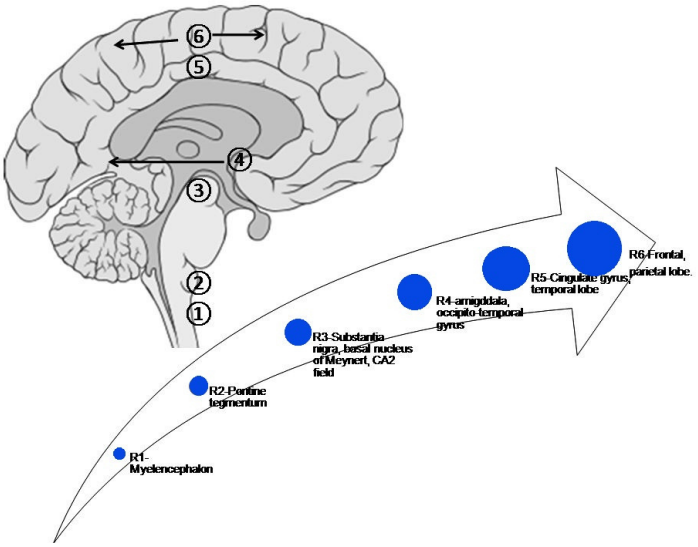

Figure 2. Staging system PD progression proposed by Braak et al. based on Keo et al. findings[5].

SLEEP CHARACTERISTICS

Sleep has an essential role in health, and around one-third of the day is usually dedicated to it. Sleep allows brain restoration when many sleep processes are carried out, such as defence against oxidative stress and clearance of waste proteins from the brain through the glymphatic system. Its lack induces many negative repercussions, e.g., in heart, kidney disease, high blood pressure, diabetes mellitus, memory loss, and stroke[1].

Most adults need around 8 hours of sleep, but with aging, due to decreased proportion of slow-wave sleep periods, the propensity to sleep, as well as its duration, decreases, and sleep become more fragmented.

Sleep progresses through 4-6 cycles, each of between 90 and 110 min, in a series of 4 stages of sleep included in two main types of sleep, with brain wave patterns particular to each one. There is Non-rapid eye movement sleep (NREM sleep – N1, N2, and N3), and REM sleep is characterized by rapid eye movement (REM), increased breathing and brain activity[1].

Within the 24 hours of the sleep-wake circadian cycle, determined by external and internal determinants, there is also the ultradian cycle – sleep phases immersed in 4-6 cycles each night. The light/dark cycle resets the activity of the suprachiasmatic nucleus (SCN), master pacemaker, via the retina and the retinohypothalamic tract. Other environmental stimuli can also entrain the SCN. Control of the peripheral clocks mainly by the central pacemaker occurs via a combination of neural and hormonal signals[1].

Paradoxical sleep is characterized by the brain and other body systems higher activation accompanied by higher muscle relaxation. This results in the expression of dreams due to increased brain activity, but with voluntary muscles immobilized. At the beginning of the night, NREM sleep is more profound and proportionally higher. However, as the night progresses, NREM sleep becomes more superficial, with a relatively higher presence of REM sleep compared to the beginning of the night.

The sleep-wake rhythm is one of the circadian rhythms that include it and almost all other bodily processes such as temperature, blood pressure, heart rate, hormone secretion, physical, mental, and behavioral changes. These rhythms respond to internal or external stimuli, mainly to ambient lighting[1].

The SCN internally controls the circadian system. It is the body's central biological clock in 24 hours of body functions. The input to SCN comes from specialized retinal ganglion cells that introduce light input and contribute to the restart of the sleep-wake cycle. However, these pathways are damaged in PD, as it occurs in dopaminergic retinal degeneration[1].

Melatonin levels increase at the end of the day, signaling the night and preparing for sleep. Sleep and basal ganglia disorders may have a common substrate, and Hasegawa et al. suggest that the latter may play an integral role in the sleep-wake cycle, specifically contributing to an oscillatory network in slow-wave sleep, which favors neural plasticity, besides the activity during REM sleep would allow the action of cognitive and emotional connections[6].

Periodic limb movement in sleep and Parkinson's disease

PD patients frequently present sleep disorders as nonmotor symptoms, which have a great impact on their quality of life. In Zhu et al's[7] cross-sectional study, approximately one-quarter of the PD patients suffered from sleep disturbances with a high prevalence of cognitive dysfunction (39.8%). In these patients, a higher percentage of sleep disorders was observed. In those with cognitive dysfunction, the nonmotor symptoms – hallucinations/delusions score was the most critical risk factor for sleep disorders. Nonmotor symptoms in early-stage PD are highly associated with the level of sleep quality[7].

The correlation between sleep disorders and PD is reinforced by studies that show REM sleep behavior disorder (RBD) as an early indicator for PD diagnosis before motor symptoms, with present data insinuating that up to 90% of patients with RBD develop some form of parkinsonism. Studies also point out that excessive daytime sleepiness may be present in both the early and late stages of PD[4].

PLMS is diagnosed on a clinical and neurophysiological basis, and it is recorded during Nocturnal Polysomnography using anterior tibialis Electromyogram (EMG) recordings. Besides, according to the American Academy of Sleep Medicine (AASM), its diagnosis may be given if the limb movements[8-12]: i. 0.5–10 sec in duration; ii. Amplitude > 8 μV above baseline; iii. In a sequence of ≥ 4 movements; iv. Onsets of consecutive leg movements ≥ 5 and ≤ 90 sec. The PLMS must be distinguished from leg movements that occur if the patient is waking up for other reasons, like sleep apnea.

Besides, there is Restless Legs Syndrome (RLS) that is commonly associated with sleep disturbance and with PLMS. PLMS and RLS are not the same. While the majority of RLS patients also have PLMS, many patients with PLMS do not have RLS. There are four main criteria for diagnosing RLS: irresistible need to move legs that feel uncomfortable; symptoms occur or worsen when there is inactivity; symptoms are relieved by moving the legs or rubbing them; symptoms worsen at night.

As already mentioned, PLMS presents as repetitive leg movement during night sleep, which is recorded through PSG (Figure 3). A study performed on 1107 subjects recruited from the German population showed, regarding PLMSI >15/hour: 32.4% prevalence, besides a positive association, in at least one of the cohorts, of factors like age, male gender, RLS, physical inactivity, current smoking, diabetes, antidepressant use and lower serum magnesium. PLMS indices were higher in men, as also occurs in PD[9].

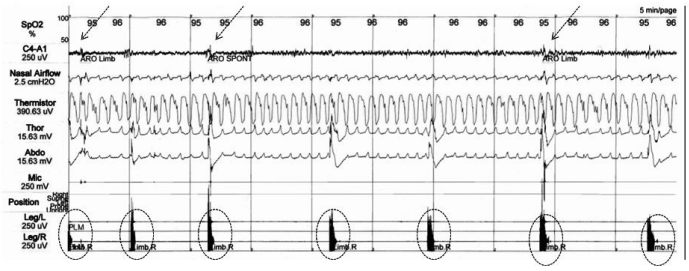

Figure 3. Periodic leg movements during sleep (PLMS) were recorded on a 5-minute polysomnogram page, demonstrating 7 PLMs (circles) with arousal peaks (arrows).

Zhang et al.[10] performed a systematic review of the literature exploring differences in PSG between PD patients and controls and they concluded that PD patients have poor quantity and quality of sleep. That work revealed an increased PLMI in PD patients when compared to healthy controls [10], and in the study by Covassin et al.[11] it was found to be more common in patients with PD of higher severity.

PLM has been suggested to be associated with a shallower and fragmented sleep in the general population, such as an increased amount of stage N1 and decreased slow-wave sleep (SWS). This is consistent with the findings that increased PLMI of PD patients is associated with increased N1 and decreased SWS percentage in PD patients when compared to controls, suggesting that PLMS is a significant contributor to PSG measured sleep abnormalities in PD patients.

The pathophysiology of PLMS is unknown, but there are reports of a negative correlation between the binding of the striatal tracer and PLMI, as reported in a study of PSG and SPECT [4]. As for the pathophysiology of PLMS during PD sleep, it is also not fully understood. However, a reduction in striatal dopamine transporter binding has been suggested in PD patients with PLMS compared to those without PLMS. Furthermore, given the importance of the dopaminergic system in sleep-wake regulation, sleep quality may be worse in parkinsonian patients with PLMS compared to those without it. Thus, the affected dopaminergic system could impact on sleep of PD patients, by increasing PLMI[10].

However, more evidence suggests common pathophysiological pathways, as nigrostriatal degeneration can promote PLMS as well as PD, and there is also a relationship between the number of leg movements and the loss of nigrostriatal dopaminergic cells. In addition, dopaminergic drugs provide benefits for PD and PLMS.

Although RLS and PD are both related to central dopaminergic dysfunction, there is no definitive evidence of an association between both conditions[4]. There is no clear pharmacological management of PLMS in PD available, but the treatment of RLS includes avoidance of medications known to exacerbate RLS and iron replacement in individuals with proven iron deficiency. Dopamine agonists are commonly used, but there is concern regarding the possibility of augmentation phenomenon[1].

CONCLUSION

There is a higher prevalence of PLMS in PD and similar pathophysiology between them.

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