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Rapid Eye Movement Sleep Homeostatic Response: A Potential Marker for Early Detection of Parkinson's Disease

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Parkinson's disease (PD) is a long-term neurodegenerative disease characterized by the presence of dopaminergic neuronal loss and dysfunction in the substantia nigra. Motor disturbance is the symptom most typically reported, including bradykinesia plus either limb rigidity, resting tremor, or postural instability [1-3]. Importantly, it has been reported that at the point when the patient meets criteria for the principal of motor disturbance, approximately 60% of substantia nigra neurons are lost [4]. Non-motor symptoms have also been observed in both PD patients as well as in related animal models, including pain, autonomic dysfunction, depression, anxiety, olfactory dysfunction, cognitive impairment and sleep disorders [5,6]. The presence and severity of these non-motor symptoms as the disease progresses exacerbate the degree of disability of PD patients. These non-motor symptoms suggest that neurodegenerative processes in PD extends beyond the substantia nigra and dopaminergic deficit [6-10]. It has been noted that before PD becomes clinically significant, neurodegeneration has been ongoing for some time. This has led to the notion of a "pre-motor" phase [11], during which non-motor manifestations and a variety of other abnormalities may offer key biomarkers of the disease process.

Among the pre-motor signs, one of the non-motor symptoms that may appear before the onset of PD is rapid eye movement (REM) sleep behavior disorder (RBD). This disturbance of sleep have become a main focus as a preclinical marker of onset of PD following the intriguing observation that changes in regulation of the sleep and wakefulness cycle may occur years before the onset of PD motor symptoms [12]. RBD is a parasomnia characterized by dream-enacting behavior occurring in REM sleep [13,14]. RBD is believed due to dysfunction of the lower brainstem nuclei that regulate REM sleep [14]. Aberrant motor activity during REM sleep is the defining characteristic of RBD. REM sleep, in healthy individuals is a state characterized by an active inhibition of motor tone [15]. While the reduction of the musculoskeletal tone during REM sleep in normal individuals can be interrupted by short periods of breakthrough motor events such as jerks or twitches, REM sleep of those with RBD is experienced with an absence of a predominance of motor quiescence, and is instead accompanied by extended periods of motor activity [16,17].

It is well-known that Lewy bodies and Lewy neurites containing aggregates of the protein α-synuclein are the classic pathologic hallmark of PD [18]. The role of α-synuclein in neuronal function is not fully understood, although there is evidence that α-synuclein has roles in synaptic membrane function, catecholamine biosynthesis and exocytosis [19]. Interestingly, it has been reported that more than 50% of RBD cases develop α-synucleinopathies similar to that what is seen in PD [20]. Together the forgoing evidence suggests that RBD can be considered a prodromal phase of PD and other neurodegenerative diseases. Indeed, 2 to 13 years following detection of RBD symptomology, 16-65% of individuals develop motor symptoms of PD [12,21-24]. Several regions in brains may be involved in both sleep disturbance and PD development. Pontine tegmentum is the one neural region involved in sleep control and shown to degenerate in PD patients [25]. There are two cholinergic nuclei in the pontine tegmentum: the pedunculopontine nucleus (PPT) and the laterodorsal tegmental nucleus (LDT). PPT and LDT provide the major cholinergic innervation of rostral and caudal targets and are believed to control much of the phenomenology of REM sleep [26]. More importantly, it has been found that PD patients exhibit degeneration of PPT and LDT neurons [27,28]. Further it has also been confirmed by morphometric analysis that around 50% of cells are loss within PPT in PD patents [28]. Furthermore, degeneration of locus subcoeruleus, which has been shown via multiple brain imaging techniques, also plays an important role in atonia, as well as in motor control during REM sleep [29-33]. Further evidence has shown that nigrocortical nigrostriatal pathways are also changed in RBD before the onset of motor symptoms [34].

The connection between inflammation and neurodegeneration disorders is well established. In our study and those of other researchers, it has been shown that infection and/or cytokine-mediated inflammation plays a critical role in PD, memory and other cognition deficiencies [35-39]. We have shown that LPS exposure in at neonates age significantly increases vulnerability of dopaminergic system to low level of neuron toxics such as rotenone later in life [35-37]. Also, cytokines such as IL-1β and TNF-α have also been reported to contribute to the PD development [36,38]. Furthermore, it has been shown that inflammatory markers are associated with sleep disorders such as RBD. Several reports showed that sleep-wake pattern and electrical activity of the brain are affected significantly, and also which is associated with elevated cytokine levels [40-43]. Esumi et al. reported the sleep deprivation induces neurodegeneration through upregulating several inflammatory factors including IL-6 and TNF-α [44]. Indeed, LPS administration changes the sleep-wake cycle in rats, increases slow wave sleep (SWS) and decreases wakefulness, and more importantly, LPS interferes with REM sleep [45-48]. Although the underlying mechanisms are still poorly understood, evidence has shown that inflammation may play an important role in the association between RBD and PD development.

Recently, melatonin has been considered as a pharmacological strategy for sleep disorders in PD in several clinical studies [48]. Melatonin plays a key role in the circadian regulation of the sleep/wake cycle and is also a strong antioxidant which can protect against neural

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damage from oxidative stress and inflammation [48]. Dowling et al. reported that melatonin treatment produced an objective improvement of nighttime sleep [49]. Medeiros et al. also reported a subjective sleep improvement (as assessed by the Pittsburgh Sleep Quality Index [PSQI]) with a low dose of melatonin in PD patients [50]. Several studies indicate that melatonin may improve RBD in PD [51-54]. However, the clinical study of exogenous melatonin treatment is still quite controversial and the underlying mechanisms are not fully clear. It has been reported that the expression of melatonin receptors, MT_1 and MT_2, are down-regulated in the substantia nigra of PD patients [55]. The release of melatonin is decrease in PD as well [56,57]. Also, neuronal cell death and PD symptoms have been relieved by melatonin administration in animal models of PD induced by neurotoxins [58-60]. As described earlier, inflammation plays an important role in RBD in PD. Accordingly, melatonin may act as an antioxidant agent that may improve REM sleep in PD by preventing oxidative stress and inflammation-induced neuron damage. In conclusion, RBD is a common pre-motor symptom in many PD patients. Early-stage exposure to inflammatory factors may contribute to the development of RBD, and eventually PD. Melatonin has been shown to improve sleep quality in several sleep disorder-related diseases, including PD. However, the possible mechanism of this improvement remains unclear.

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