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Poor nighttime sleep is positively associated with dyskinesia in Parkinson's disease patients

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ABSTRACT

Background: Dyskinesia is a troublesome complication of long-term dopaminergic medications in Parkinson's disease (PD) patients. Many factors are reported to be associated with dyskinesia in PD.
Objective: To investigate the association between sleep quality and dyskinesia in patients with PD.
Methods: Four hundred twenty-five patients with PD were enrolled in this study. Demographic information was collected. Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr (H-Y) stage scale were also performed. Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) were applied to evaluate daytime sleepiness and overall nighttime sleep quality, respectively, in PD patients.
Results: Patients with dyskinesia tended to have a longer duration of disease, higher daily levodopa-equivalent dose (LED), H-Y stage, UPDRS II and PSQI score, and a higher percentage of levodopa treatment than those without dyskinesia. After adjusting for age, sex, age at onset of PD, disease duration, UPDRS I, UPDRS II, UPDRS III, cigarette smoking, use of different antiparkinsonian drugs, phenotype, daily LED, and restless leg syndrome (RLS), PSQI score was still associated with dyskinesia, with corresponding ORs 1.111 (95% CI, 1.004−1.229) as a continuous variable, and 2.469 (95% CI, 1.051−5.800) as a categorical variable, respectively. Further analysis of PSQI components showed that subjective sleep quality and sleep latency were associated with dyskinesia in PD patients.
Conclusions: Our data showed that poor nighttime sleep is positively associated with dyskinesia in PD patients. Attention to the management of nighttime sleep quality may be beneficial to dyskinesia in patients with PD.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, and is characterized by motor and non- motor dysfunction [1]. Although Levodopa is the most effective agent for the symptomatic treatment of PD, the emergence of side effects, particularly motor fluctuations and dyskinesia, can limit its use in some patients [2]. Though its incidence rate differs between western countries and eastern countries, dyskinesia seriously affects patients' quality of life [2–4]. The pathogenesis of dyskinesia is unknown. Multiple lines of evidence show that Levodopa-induced dyskinesia (LID) is associated with neurodegeneration in cortical and subcortical areas, including prefrontal cortex, primary motor cortex (via the pallidothalamocortical motor pathway), striatum, subthalamic nucleus, and cerebellum. Dysregulation of neurotransmitters other than dopamine, such as serotonin, γ-

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aminobutyric acid (GABA), glutamate, adenosine, and acetylcholine is also implicated in dyskinesia [5]. Changes in cellular signaling pathways and enhanced dopamine D1 receptor stimulation resulting in widespread molecular adaptations in striatal medium spiny neurons, play important roles in LID [6]. Uncontrolled long-term potentiation (LTP) of corticostriatal synapses is also associated with the development of LID [7]. Other risk factors that have been identified related to dyskinesia in PD patients include a younger age of onset, longer duration of levodopa therapy, female sex, disease duration, and the total daily levodopa dose [4,5,8].

Disordered sleep is one of the most frequent non-motor symptoms in PD patients, and has a significant negative impact on quality of life [9]. In PD patients, sleep disorders include insomnia, vivid dreams, restless legs syndrome (RLS), rapid eye movement sleep behavior disorder (RBD), periodic limb movements (PLM), circadian rhythm disruption and excessive daytime sleepiness (EDS) [10]. The etiology of sleep disorders in PD are likely to be multifactorial. Potential contributing factors include degeneration of central sleep regulatory areas, adverse effects of anti-parkinsonian medications, age-related sleep changes, and the impact of motor symptoms (nighttime akinesia, dyskinesia, tremor, and rigidity) [9]. Degeneration of multiple areas of the central nervous system involving various neurotransmitters is associated with sleep disorders in PD, including the dopaminergic ventral tegmental area, serotonergic dorsal raphe nuclei, noradrenergic locus coeruleus and dorsal nucleus of the vagal nerve, and cholinergic laterodorsal tegmental nucleus and pedunculopontine nucleus [11].

Recently, some studies have shown that slow homeostatic adjustment of intrinsic excitability occurring during sleep was very important for network stabilization [12]. Spike-timing-dependent plasticity such as LTP has a crucial role in network stability. Slow-wave activity (SWA) is considered to be the basis for overnight homeostatic processes, and is associated with spike-timing-dependent plasticity. Impaired synaptic homeostasis during sleep correlated with dyskinesia in an animal model of PD [7]. Furthermore, “sleep benefit” on motor symptoms was observed in the morning in PD patients [13]. Common impaired brain regions and altered neurotransmitters, as well as the “sleep benefit” phenomenon, suggest a correlation between sleep and dyskinesia among PD patients.

So far, the association of sleep and LID in PD patients has not been investigated. Therefore, in this study, we aim to investigate the relationship between sleep disorders and dyskinesia in PD patients.

2. Methods

2.1. Subjects

A total of 425 PD patients were enrolled in this study at the Second Affiliated Hospital of Soochow University from Jan 2014 to Dec 2016. The clinical diagnosis of idiopathic PD was determined based on UK Parkinson's disease Brain Bank criteria [14]. Demographic information, including age, sex, disease duration, concurrent diseases, medication information for PD and other diseases such as hypertension and diabetes mellitus, and detailed medical history, was collected. All the subjects were carefully evaluated by a movement disorder specialist. Unified Parkinson's disease rating scale (UPDRS) and Hoehn & Yahr stage (H-Y stage) scale were applied to all PD subjects during the medication “on” state [15,16]. PD subjects were classified as tremor-dominant (TD) subtype, akinetic-rigid (AR) subtype, or mixed subtype using the numerical ratio, which was derived from a patient's mean tremor score and mean akinetic-rigidity score. The tremor score was derived from the sum of a 7-item scale that included action or postural tremor of the hands (two items) and rest tremor of the face/lips/chin and each limb (five items). The non-tremor score was also derived from the sum of a 12-item scale that included passive range of motion, rigidity of the neck and each extremity (5 items), facial expression and speech (2 items), rising from a chair (1 item), posture and postural instability (2 items), gait (1 item), and body bradykinesia (1 item). Each item was rated 0–4 with 0 representing the absence of symptoms. The mean of each scale was calculated and then the ratio (mean TD/mean AR score) determined. Based on this method, AR subjects had a ratio <0.8, whereas TD subjects had a ratio >1.0, and mixed subjects had a ratio range from 0.8 to 1 [17].

Dyskinesia was assessed using UPDRS Part IV based on item 32. Item 32: “What proportion of the waking day is dyskinesia present? (historical information)”, where a score of 0 = none, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, and 4 = 76–100%. Dyskinesia was defined as present if the response to UPDRS IV item 32 was ≥1.

Calculation of a daily levodopa equivalent dose (LED) for each patient was based on theoretical equivalence to levodopa as follows: levodopa dose + levodopa dose × 1/3 if on entacapone + piribedil (mg) + pramipexole (mg) × 100 + selegiline (mg) × 10 + amantadine (mg) + controlled release levodopa (mg) × 0.75.

Epworth Sleepiness Scale (ESS)(a measure of daytime sleepiness) and Pittsburgh Sleep Quality Index (PSQI) (a measure of the quality of nighttime sleep over the previous month) were completed by each PD patient [18,19]. The 8-item ESS is a useful and widely used questionnaire for assessing general level of daytime sleepiness. The scale comprises eight items that address typical day-to-day situations. Each item can range from 0 to 3 points (0 = would never doze, 3 = high chance of dozing). The total ESS score is from 0 to 24 (lowest to highest sleep propensity). The proposed range for normal sleep propensity is 0–10. The Chinese version of Epworth sleepiness scale also appears to have good internal consistency and reliability among Mandarin-speaking subjects as a standardized screening test of sleepiness in daily life, with the same cut-off value [20]. The PSQI is a self-report questionnaire that assesses sleep quality over a 1-month time period. Nineteen individual items generate seven ‘component’ scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The scores for these components range from 0 (no difficulty) to 3 (severe difficulty) and are summed to produce a global measure of sleep disturbance, with a score ranging from 0 to 21. Higher scores represent poorer subjective sleep quality. The Chinese version of PSQI showed good validity and reliability for assessment of sleep quality in the Chinese population. The highest sensitivity and specificity of PSQI for evaluating sleep disorders in the Chinese population were obtained when using a cut-off value of 7.5, with a sensitivity of 88% and a specificity of 84% [21]. So in this study, subjects with PSQI >7 were considered as poor sleepers. Diagnosis of RLS was made according to the RLS diagnostic criteria proposed by the International Restless Legs Syndrome Study Group (IRLSSG) in 2014 [22].

All patients received dopaminergic medications.

Subjects were excluded if they had a secondary parkinsonism syndrome, atypical parkinsonian syndrome, malignant neoplasm, epilepsy, or severe cardiopulmonary disease.

This study was approved by the ethics committee of the Second Affiliated Hospital of Soochow University and informed consent was obtained from all participants.

2.2. Statistics

The study participants were divided into two groups, those with and those without dyskinesia. Continuous variables were expressed

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