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The combined effect of REM sleep behavior disorder and hyposmia on cognition and motor phenotype in Parkinson's disease

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ABSTRACT

Background: Olfactory dysfunction and REM sleep behavior disorder (RBD) are recognized as pre-motor symptoms of Parkinson's disease (PD). Cognitive dysfunction is observed at a high rate even in the early stages of PD as an important non-motor symptom. PD has been classified in different subtypes and it is unknown if olfactory dysfunction and RBD occur more often in one particular subtype. We investigated the relationship between olfactory impairment, RBD, initial cognitive performance and motor phenotype in PD.

Method: Nighty-eight patients with drug-naïve idiopathic PD who visited the Movement Disorders Unit of Korea University Guro Hospital, Seoul, Korea from March 2012 to February 2014 were retrospectively included. Patients were divided into tremor-dominant-type and akinetic-rigid-type PD subgroups using part III of the Unified Parkinson's Disease Rating Scale. Olfaction was assessed by the Cross Cultural Smell Identification Test. RBD was screened using screening questionnaires. Initial cognitive function was assessed with Mini–Mental State Examination.

Result: The PD-normosmia group had higher MMSE scores ($p = 0.008$). PD patients who have both RBD and olfactory dysfunction had lower MMSE scores ($p = 0.013$). Presence of both RBD and hyposmia in PD patients was more strongly correlated with poor cognitive dysfunction. PD patients with RBD and/or hyposmia primarily exhibited the akinetic-rigidity phenotype.

Conclusion: Olfactory dysfunction and RBD differed according to the motor phenotypes of PD. This suggests that olfactory dysfunction and RBD might relate to prognosis in patients with PD. Patients who have both hyposmia and RBD were more likely to exhibit cognitive dysfunction.

1. Introduction

Although it was initially thought that intellect was unaffected in Parkinson's disease (PD) [1], it has recently become apparent that specific cognitive dysfunctions are observed at a high rate even in the early stages of PD [2]. Such dysfunction gradually worsens with disease progression and eventually leads to dementia in approximately 80% of cases [3,4]. In addition, it has been suggested recently that Parkinson's disease with dementia (PDD) is one of the biggest risk factors of mortality in PD [5], highlighting the importance of effectively managing PDD.

The pathophysiology of hyposmia in PD is poorly understood. Neuronal degeneration with deposition of α-synuclein within the olfactory bulb, anterior olfactory nucleus and limbic rhinencephalon occurs early in PD [6]. A recent positron emission tomography study of 58 patients with PD found relatively strong correlations between scores on a 40-item smell identification test and the activity of acetylcholinesterase, the enzyme that breaks down acetylcholine, in the hippocampus, amygdala and neocortex [7]. Such an association suggests a close relationship between olfactory function and central cholinergic processes in PD. These results suggest that olfactory dysfunction may be correlated with cholinergic abnormalities in the hippocampus, amygdala and neocortex [8]. We hypothesis that olfactory dysfunction would correlate closely with initial cognitive dysfunction in PD.

REM sleep behavior disorder (RBD), first described by Schenck and colleagues in 1986 [9], is characterized by the loss of normal muscle atonia during REM sleep with prominent motor activity and dreaming. Abnormal neural circuits resulting from damage to pontomedullary brainstem areas may have precipitated idiopathic RBD leading to the loss of motor inhibition during rapid eye movement (REM) sleep [10]. Idiopathic RBD is regarded as a prodromal stage of Parkinson's disease because it often precedes the development of motor, cognitive, neuropsychiatric and autonomic features of these syndromes by years or decades [11]. Recently, Schenck and colleagues reported that over 80% of males aged 50 years and older initially diagnosed with idiopathic RBD developed a neurodegenerative disorder, with the vast majority being diagnosed with PD [12]. Rolinski's group studied the association between RBD and non-motor features in early PD [13]. Their results

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suggest that patients with concomitant RBD are more likely to have worse cognitive function. We investigated the association between RBD and initial cognitive function in PD.

There are several reports that suggest that patients with the akinetic rigidity phenotype exhibit more cognitive impairments compared to tremor-dominant PD patients [14]. We hypothesize that olfactory dysfunction and RBD are associated with motor phenotype PD, and thus that olfactory dysfunction and RBD are correlated with poor cognitive function in PD.

In this study, we examined the association between cognitive function, the presence of olfactory dysfunction, and RBD as well as the relationship between motor phenotype and the presence of olfactory dysfunction. Additionally, we investigated the difference in cognitive function and motor phenotype according to the presence or absence of olfactory dysfunction and RBD in PD patients.

2. Patients and methods

2.1. Subjects

We recruited consecutive drug-naïve PD patients from the Movement Disorders Unit of Korea University Guro Hospital, Seoul, Korea from March 2012 to February 2014. All patients met the clinical diagnostic criteria for PD, as described by the United Kingdom Parkinson's Disease Society Brain Bank [15]. We obtained brain MRI to exclude secondary parkinsonism and/or Parkinson plus syndrome. Patients who had brain lesions on MRI were excluded.

To ascertain dopaminergic drug treatment response, we reviewed the medical records of all included patients over two years. Exclusion criteria were as follows: (1) a history of head trauma, stroke, exposure to anti-dopaminergic drugs, or central nervous system (CNS) infection; (2) structural lesions or hydrocephalus on brain MRI; (3) red-flag signs suggesting Parkinson plus syndrome and (4) history of rhinitis, sinusitis, nose surgery. The study flow chart is presented in Supplementary Fig. 1. Of the 141 patients who met the clinical diagnostic criteria for PD, 122 were drug naïve PD patients. 106 patients had no structural lesions on brain MRI and 98 patients had olfactory function assessed by the Cross-Cultural Smell Identification Test (CCSIT). The present study was approved by the Institutional Review Board of the Korea University Guro Hospital.

2.2. Clinical assessment

Patients underwent neurologic examination and clinical assessment. Symptom history, level of education, comorbid diseases and medication history were assessed. The Hoehn and Yahr (H&Y) stage was determined [16], and the degree of disease severity was quantified by the Unified Parkinson's Disease Rating Scale (UPDRS) [17].

We assessed olfactory function using the CCSIT. The 12-item CCSIT (Sensonics, Inc., Haddon Heights, NJ) was used for the assessment of olfactory function [18]. Hyposmia was defined as the test scores lower than the reference value of the articles presented by Doty [18]. This test consists of a booklet, each containing a micro-encapsulated odorant that is released by scratching the bottom box with a pencil tip.

RBD was screened with RBD screening questionnaires [19]. The general cognitive status of each subject was evaluated by means of the Mini–Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) scale at baseline.

PD subjects were classified as either tremor-dominant or akinetic-rigid type using the modified ratio based on the UPDRS-III [20]. Namely, a numerical ratio was derived from a patient's mean tremor score and mean akinetic-rigidity score. Tremor was assessed using a nine-item scale that included history of left or right tremor (two items), rest tremor of the face/lips/chin and each limb (five items), as well as postural tremor of the right and left upper extremities (two items). The 12-item akinetic-rigidity scale assessed passive range of motion rigidity of the neck and each extremity (five items), rapid opening/closing of the hands (one item), finger tapping (one item), rising from a chair (one item), posture and postural instability (two items), gait (one item), and body bradykinesia (one item). Each item was rated 0–4 with 0 representing absence of symptoms/normal activity and 4 representing significant presence of the symptom or impairment. The mean of each scale was calculated and then the ratio (tremor/akinetic-rigidity score) determined. Using this method, tremor-dominant-type patients will have a ratio > 1.0, whereas akinetic-rigid-type patients will have a ratio < 1.0.

2.3. Statistical analysis

Analysis of descriptive variables was performed using non-parametric analysis (Mann–Whitney *U* test, Kruskal–Wallis test) and χ^2 tests for continuous and ordinal variables, respectively. Post hoc comparisons were carried out using the Mann–Whitney *U* test. The MMSE score was analyzed with analysis of covariance (ANCOVA) including confounders, such as age, education level, modified H&Y score. The cut-off for statistical significance was defined as $p < 0.05$. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) 17.0 for Windows.

3. Results

3.1. Baseline and clinical characteristics

A total of 98 patients were enrolled in the study. The demographic and clinical characteristics are shown in Table 1. Patients with hyposmia were of significantly older age and higher H&Y score. Other variables such as gender distribution, education level, and duration of PD symptoms were comparable between the hyposmia group and normosmia group. Patients with RBD had significantly higher H&Y scores, but other variables such as gender distribution, age, education level, duration of PD symptoms were comparable between the two groups. Table 2 illustrates the clinical characteristics of the three groups according to the presence or absence of two factors, hyposmia and RBD. There were no differences in gender, age, education level or disease duration between the groups. The patients who had both factors had a significantly higher H&Y score than the other two groups.

3.2. Relationship of MMSE score and olfactory dysfunction & RBD

The PD-normosmia group had significant higher MMSE scores compared to the PD-hyposmia group ($p = 0.016$). Although the PD-non RDB group tended to score higher on the MMSE, this was consistent with chance ($p = 0.072$) (Table 1, Supplementary Fig. 2). There were significant differences in MMSE scores between the groups according to the presence of hyposmia and RBD ($p = 0.013$) (Table 2). Patients who exhibited both factors had significant lower initial MMSE scores than patients who had neither factor ($p = 0.005$). There were significant differences in MMSE score between the normosmia/non-RBD group and hyposmia/RBD group ($p = 0.008$) (Supplementary Table 1). However, univariate ANCOVA analysis showed confounders such as age, education level and modified H&Y did not significantly affect MMSE scores between the hyposmia and normosmia groups.

3.3. Relationship of the motor type of PD and olfactory dysfunction & RBD

Twenty eight (88%) patients among the normosmia group ($n = 32$) and 30 (46%) patients among the hyposmia group ($n = 66$) had tremor dominant phenotype (odds ratio = 8.4, $p < 0.001$). Thirty eight (69%) patients among the non-RBD group ($n = 55$) and 20 (47%) patients among the RBD group ($n = 43$) had tremor-dominant phenotype (odds ratio = 2.57, $p = 0.024$) (Fig. 1).