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Association of coffee consumption and non-motor symptoms in drug-naïve, early-stage Parkinson's disease

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ABSTRACT

Objective: Coffee consumption has an inverse association with the risk of Parkinson's disease (PD). The aim of this study was to investigate the association between coffee consumption and non-motor symptoms (NMSs) in patients with PD.
Methods: In this cross-sectional study, we included 196 early-stage, treatment-naïve PD patients. Coffee consumption history was obtained via semi-structured interviews. NMSs were assessed using the Non-Motor Symptom assessment scale (NMSS).
Results: Of the 196 patients with PD, 136 (69.3%) were categorized as coffee drinkers and 60 (30.6%) were non-drinkers. Coffee drinkers were younger, predominantly male, were younger in age at symptom onset, had lower Unified Parkinson's Disease Rating Scale motor and Beck Depression Inventory scores, and higher Mini-Mental State Examination scores than non-coffee drinkers. After adjustment, coffee drinking was significantly inversely associated with the prevalence of lack of motivation, anhedonia, and lack of pleasure, which were less frequent in coffee drinkers. Total NMSS scores were lower in coffee drinkers than in non-drinkers ($p = 0.047$). In particular, coffee drinking was significantly associated with a reduced severity of the mood/cognition domain of NMSS ($p = 0.003$). After correcting for multiple testing, there were no significant differences in the prevalence of NMSs, but there were significant differences in the severity of NMSs between coffee drinkers and non-drinkers.
Conclusion: There is a negative association between coffee consumption and the severity of the mood/cognition domain of NMSS in patients with PD. Clinicians should consider the history of coffee consumption in the assessment of NMSs in PD.

1. Introduction

Non-motor symptoms (NMSs) of Parkinson's disease (PD) can precede the emergence of typical motor symptoms and the diagnosis of PD by several years [1]. NMSs often have a significant adverse effect on the quality of life of PD patients [2]. Understanding NMSs is important in order to reveal the underlying pathophysiology of PD and to define an at risk population for future PD prevention trials [1]. NMSs, encompassing olfactory and memory dysfunctions, sleep abnormalities, and depression are common in PD, although these symptoms are often not well recognized in clinical practice. Even movement disorder specialists often concentrate on the management of motor symptoms and motor complications such as dyskinesia [3]. However, considering the comprehensive management of PD patients, it is important to recognize and manage NMSs [4]. Assessment of NMSs in a structured, unified, and integrated manner may be a key issue in considering future neuroprotection and clinical trials [5].

An inverse association between coffee consumption and the risk of PD has been reported in several studies [6–9]. This association is supported by a study that showed caffeine, a major chemical component of coffee, attenuated the loss of striatal dopamine and dopamine transporter binding sites in an experimental mouse model of PD [10]. Furthermore, coffee consumption seems to have an inverse association with the motor symptoms of PD, as demonstrated in diverse experimental models of PD [11,12].

In spite of the well-known inverse association between coffee consumption and the risk of PD, there is lack of reports on the association between coffee consumption and NMSs in patients with

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PD, especially in early-stage, drug-naïve patients. Therefore, we examined, prospectively, the association between coffee consumption and the prevalence and severity of NMSs in early-stage, treatment-naïve PD patients.

2. Methods

2.1. Study population

We conducted a baseline evaluation to determine the prevalence and severity of NMSs and the association with coffee consumption in a cohort of early-stage, treatment-naïve PD patients. One hundred ninety-six newly diagnosed, untreated PD patients participated in the study. They were all out-patients from the Movement Disorders Clinic at Chonnam National University Hospital and were consecutively enrolled from January 2011 to December 2015.

According to the international criteria, the diagnosis of PD included two steps [14], the definition of parkinsonism as a syndrome and the definition of PD within the syndrome. Parkinsonism was defined by the presence of bradykinesia plus one other sign i.e., muscular rigidity, 4–6 Hz rest tremor, or postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction. The clinical diagnosis of PD was based on the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria [13]. An additional criterion for inclusion in our study was a lack of significant cerebral lesions, assessed via brain magnetic resonance imaging (MRI). All patients had no history of present or past therapy with antiparkinsonian agents and none of the patients were on any medications with known antidopaminergic effects. Exclusion criteria were unclear diagnosis, secondary (such as vascular and drug-induced) or atypical (such as multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, and dementia with Lewy bodies) parkinsonism according to current diagnostic criteria [14–17], inability to complete the questionnaire related to NMSs or coffee consumption, and dementia. Onset of PD was defined as the year in which one of the four cardinal signs of PD was first noted by the patient, by family members, or by a caregiver (as recorded in the patient's medical record).

All the participants provided their written informed consent to participate in this study. The study was approved by the Institutional Review Board of the hospital and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

2.2. Clinical evaluation

All patients with PD were diagnosed by a movement-disorder specialist (S.M.Choi). Detailed clinical information was obtained from the patient's history and neurological examination. The severity and stage of the patient's parkinsonism were assessed using the modified Hoehn and Yahr stage scale and the motor (part III) and activities of daily living (ADL; part II) subscores of the Unified Parkinson's Disease Rating Scale (UPDRS).

For evaluation of NMSs of PD patients, the Non-Motor Symptom assessment scale (NMSS) for PD was used [18,19]. The NMSS evaluates 30 non-motor symptoms in PD. Included items are organized into nine domains. Scores are assigned by a professional rater during an interview with the patient and/or caregiver. Each item evaluates frequency and severity separately and scores from 0 (not present) to 12 (maximum frequency and severity) by multiplication of both measures ("symptom burden"). The severity and frequency of these items were measured according to the following rubric Severity: 0 = None, 1 = Mild (symptoms present but causes little distress or disturbance to patient), 2 = Moderate (some distress or disturbance to patient), 3 = Severe (major source of distress or disturbance to patient). Frequency: 1 = Rarely (<1/week), 2 = Often (1/week), 3 = Frequent (several times per week), 4 = Very Frequent (daily or all the time). The total scores for the domains were obtained by the sum of the corresponding item scores, and for the total scale by the sum of the domains [18]. In addition to NMSS, scores of the Beck Depression Inventory (BDI) for depressive mood [19] and the Korean version of Mini-Mental State Examination (K-MMSE) for cognitive functions were also obtained via interviews [20].

History of coffee consumption and current coffee drinking status were collected by a semi-structured interview. Briefly, the interview was composed of several questions; 1) Have you ever drunk coffee or do you drink coffee currently? 2) If you have ever drunk coffee, from what age did you start drinking coffee? 3) How long have you drunk coffee for? 4) On average, how many times a day do you have coffee? 5) If you have stopped drinking coffee, how long have you been abstinent? For our analyses, we considered participants in two groups, ever coffee drinking versus never drinking coffee.

2.3. Statistical analysis

The results are presented as the mean and standard deviation (SD) for continuous variables and the number and percentage for categorical variables. Bivariate analyses (Student's t-test, Mann-Whitney *U* test, or chi-square test depending on the data distribution) were used to compare the demographic and clinical variables between PD patients with a coffee drinking history and those without. Analysis of an association between coffee consumption and prevalence of NMSs was carried out using a multivariate stepwise logistic regression analysis. Adjustments were made for demographic and clinical variables, which were shown to be significantly different between non-coffee drinkers and coffee drinkers via bivariate analyses. Analysis of covariance (ANCOVA), controlling for the effects of demographic and clinical variables which were significantly different, was used to compare the severity of NMSs between PD patients with a coffee drinking history and those without. The p-values for each item or domain were corrected for by multiple testing using the false discovery rate. Statistical analyses were performed using SPSS software (version 22.0, IBM corp., Armonk, NY, USA). P-values of less than 0.05 were considered significant.

3. Results

3.1. Demographic and clinical findings

One hundred thirty-six (69.39%) of the 196 PD patients were categorized as coffee drinkers (Coffee drinker group) and 60 (30.61%) were non-coffee drinkers (Non-coffee drinker group). The intergroup comparisons revealed that coffee drinkers were younger, predominantly male, and were younger in age at typical motor symptom onset, with statistical significance. Coffee drinkers had significantly lower UPDRS motor scores ($p = 0.020$), lower NMSS scores ($p = 0.002$), lower BDI scores ($p = 0.014$), higher MMSE scores ($p = 0.004$) and longer formal education periods ($p = 0.002$) than non-coffee drinkers. The two groups did not differ in terms of other demographic and clinical variables (Table 1).

3.2. Prevalence of NMSs

The prevalence of NMSs is shown in Table 2. In both groups, sleep/fatigue symptoms were most prevalent out of the 9 domains of NMSS. Urinary, attention/memory, mood/cognition, and

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