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Subjective cognitive decline predicts future deterioration in cognitively normal patients with Parkinson's disease

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ABSTRACT

Increasing evidence suggests that subjective cognitive decline (SCD) is a potential predictor of future cognitive decline or dementia. We investigated whether SCD in patients with Parkinson's disease (PD) is a predictor of future cognitive decline. Forty-six cognitively normal patients with PD were selected using comprehensive neuropsychological tests, and classified depending on the presence (PD-SCD$^+$, n = 25) or absence of SCD (PD-SCD$^-$, n = 21). After a mean follow-up of 2.4 years, we repeated the cognitive assessments with the same subjects. The clinical characteristics and cognitive performance of the 2 groups did not differ at baseline. At the follow-up assessment, 11 patients in the PD-SCD$^+$ group (44.0%) and 2 in the PD-SCD$^-$ group (9.5%) were diagnosed with mild cognitive impairment (MCI), and the PD-SCD$^+$ patients showed more rapid decline in semantic fluency and visuospatial memory tasks than those in the PD-SCD$^-$ group. A multivariate logistic regression analysis showed that presence of SCD (odds ratio, 8.378; 95% confidential interval, 1.472–47.683, $p = 0.017$) and higher Unified PD Rating Scale motor score of 20 or more (odds ratio, 4.539; 95% confidential interval, 1.004–20.528; $p = 0.049$) were risk factors for incident MCI. Present results demonstrate that SCD in cognitively normal patients with PD is an independent risk factor for incident MCI and acts as a predictor for future cognitive decline.

1. Introduction

Subjective cognitive decline (SCD) is a common manifestation in old age (Jonker et al., 2000). Recent longitudinal studies indicate that SCD is a predictor of future cognitive decline or development of dementia (Geerlings et al., 1999; Jorm et al., 2001; Wang et al., 2004), whereas others report that SCD is associated with depression or personality traits rather than cognitive decline (Hanninen et al., 1994; Jungwirth et al., 2004; Minett et al., 2005). Although its predictive value remains controversial, several anatomic (Jessen et al., 2006; Striepens et al., 2010), pathologic (Barnes et al., 2006; Perrotin et al., 2012), and biochemical studies (Stomrud et al., 2007) also reported that SCD is associated with the neurodegenerative process of Alzheimer's disease (AD).

Parkinson's disease (PD) was originally defined by motor symptoms, however, dementia is a common and the most disabling feature in patients with PD (Schrag et al., 2000). The prevalence of dementia varies (Aarsland et al., 2003; Hely et al., 2008; Williams-Gray et al., 2007), but the highest reported rate is up to 80% (Aarsland et al., 2003). Similar to mild cognitive impairment (MCI) in AD, MCI in patients with PD (PD-MCI) is considered a risk factor for the development of dementia (Janvin et al., 2006; Williams-Gray et al., 2007). In terms of SCD in patients with PD, even though the concept and its clinical significance is not settled, we reported previously that patients with PD and SCD have more cortical atrophy and perform more poorly on neuropsychological tests than those without SCD, suggesting that SCD in patients with PD is possibly related to PD-related pathologic changes (Hong et al., 2012). Additionally, another cross-sectional study showed that both self-rating and proxy-rating subjective memory functions were correlated with objective cognitive performance in patients with PD (Sitek et al., 2011). However, the clinical significance of these studies are limited in the cross-sectional design, thus, a prospective study is required to determine the role of SCD as a predictor of future cognitive decline in patients with PD. In the present study, we recruited cognitively normal patients with PD and prospectively followed their cognitive changes for mean 2.4 years to investigate whether the SCD is a risk factor for future cognitive decline in cognitively normal patients with PD.

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2. Methods

2.1. Subjects

We reviewed the medical records of the movement disorders outpatient clinic at Yonsei University Severance Hospital, and selected cognitively normal patients with PD. PD was diagnosed following the clinical diagnostic criteria of the UK PD Society Brain Bank (Gibb and Lees, 1988), and cognitive performance was evaluated using the Korean version of Mini-Mental State Examination (K-MMSE) and comprehensive neuropsychological tests at the diagnosis of PD. Definition of normal cognition is described in the following. We excluded the patients with focal brain lesions or multiple lacunar infarctions in the basal ganglia based on magnetic resonance imaging or possible medical comorbidities affecting cognition by laboratory testing including thyroid function tests, vitamin B_{12} and folic acid levels, and a screening test for syphilis. Patients with a history of drug use causing parkinsonian symptoms were also excluded. Among 58 patients who were selected with records, 5 patients were lost to follow-up, and 5 patients underwent the deep-brain stimulation. Brain tumor was found in another patient, and 1 patient refused to attend this study. Excluding these 12 patients, 46 subjects were recruited in the study.

We classified the subjects into PD-SCD$^+$ (n = 25) and PD-SCD$^-$ (n = 21) groups depending on the presence or absence of SCD, which was assessed by the question to the patients at baseline neuropsychological assessment: "Do you feel that you have a declining memory?" Their cognitive performances were evaluated again to a mean follow-up of 2.4 (1.3–4.3) years from the baseline assessment.

We received approval from the Yonsei University Severance Hospital ethical standards committee on human experimentation for the use of human subjects. Written informed consent was obtained from all subjects participating in this study.

2.2. Clinical assessment

Parkinsonian motor symptoms were assessed using the Unified PD Rating Scale (UPDRS) motor score. A score for general white matter hyperintensities (WMHs) was determined by grading the extent of the increased white matter signal intensity on fluid-attenuated inversion recovery images in the periventricular and subcortical white matter. It was graded on a 10-point scale from 0 to 9, with a higher score indicating a more severe white matter grade (Yue et al., 1997). The self-rated Beck Depression Inventory (BDI) was used to assess depressive symptoms in patients with PD, and a score above 16 was considered as major depression (Jo et al., 2007).

2.3. Cognitive assessment

Baseline and follow-up cognitive assessments were conducted by experienced neuropsychologists using the K-MMSE and the Seoul Neuropsychological Screening Battery (Kang and Na, 2003; Lee et al., 2010a, 2010b). We selected the following cognitive subsets from the Seoul Neuropsychological Screening Battery according to the recommendation of diagnostic criteria for PD-MCI proposed by the Movement Disorder Society Task Force (Litvan et al., 2012): attention (digit span and the color stroop test), language functions (the Korean version of the Boston Naming Test), visuospatial function (the Rey Complex Figure Test copying), memory (verbal memory, 20-minutes delayed recall using the Seoul Verbal Learning Test; visual memory, 20-minutes delayed recall using the Rey Complex Figure Test), and executive function (semantic and phonemic fluency using the Controlled Oral Word Association Test). Score below the 16th percentile (1 standard deviation below mean) of the age- and education-appropriate norms for each item were considered abnormal.

2.4. Definition of cognitively normal patients and diagnosis of MCI at follow-up

At the baseline and follow-up assessment, when a subject scored above the 16th percentile for their age- and education-appropriate norm on the K-MMSE and showed impairment on less than 2 items of neuropsychological test, this subject was regarded as cognitively normal.

Additionally, these participants showed no evidence of abnormal activities of daily living (ADL), judged both clinically and on an instrumental ADL scale (Kang et al., 2002).

MCI at the follow-up assessment was diagnosed according to the criteria for PD-MCI proposed by the Movement Disorder Society (level I category) (Litvan et al., 2012). MCI was defined if at least 2 items were abnormal without evidence of abnormal ADL.

Additionally, we calculated the annual rate of cognitive decline by dividing the change in the performance score between the baseline and follow-up assessments by the interval between the 2 assessments.

2.5. Statistical analysis

The χ^2 test and Fisher's exact test were used for categorical variables, and the independent *t* test and the Mann-Whitney U test were conducted for continuous variables. The multivariate analysis of covariance was adopted for comparing cognitive change with age, years of education, BDI score, and logarithmically transformed disease duration of PD as covariates. Stepwise logistic regression analysis was used to reveal predictors of incident MCI. Statistical analyses were performed using SPSS Statistics 20 (IBM SPSS, Armonk, NY, USA), and a $p < 0.05$ was considered significant.

3. Results

3.1. Baseline demographic and neuropsychological characteristics

The baseline characteristics of the subjects are shown in Table 1. Mean disease duration of PD and UPDRS motor scores of study subjects were 3.0 years (range 0.2–11.6 years) and 19.3 points, respectively. No significant differences were observed between the PD-SCD$^+$ and PD-SCD$^-$ groups in terms of age, sex, duration of

Table 1
Baseline characteristics of patients with Parkinson's disease according to the presence or absence of subjective cognitive decline

	PD-SCD$^+$ (n = 25)	PD-SCD$^-$ (n = 21)	*p* value
Age	66.6 ± 6.8	65.7 ± 7.2	0.685[a]
Number of male, n (%)	8 (32.0)	7 (33.3)	0.923[c]
Duration of motor symptom, (y)	3.5 ± 0.7	2.3 ± 2.1	0.279[b]
Years of education	9.5 ± 5.1	9.0 ± 6.3	0.789[a]
BDI score	16.3 ± 9.9	16.1 ± 10.9	0.952[a]
UPDRS motor score	20.4 ± 7.2	18.0 ± 9.6	0.322[a]
White matter hyperintensity score	1.7 ± 1.5	1.7 ± 1.2	0.910[b]
Baseline K-MMSE score	27.2 ± 2.0	27.6 ± 2.4	0.278[b]

Data are expressed as mean ± SD.
Key: BDI, Beck's depression inventory; K-MMSE: Korean version of Mini-mental state examination; PD, Parkinson's disease; SCD, subjective cognitive decline; UPDRS, Unified Parkinson's disease rating scale.
[a] Independent *t* test.
[b] Mann-Whitney U test.
[c] χ^2 test.