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Effect of olfactory impairment and white matter hyperintensities on cognition in Parkinson's disease

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ABSTRACT

Introduction: Although white matter hyperintensities (WMH) and olfactory dysfunction are independently associated with the cognitive impairments in Parkinson's disease (PD), the effects of simultaneous presence of these abnormalities remain unknown. Thus, we investigated the different effects of deep WMH and periventricular WMH on olfactory and cognitive performance and evaluated the additive effects of the concurrent presence of WMH and olfactory dysfunction on cognitive performance in PD.
Methods: We enrolled 171 patients with non-demented PD whose WMH scores were assessed using a semi-quantitative visual rating system. The olfactory and cognitive performance was assessed using the Cross-Cultural Smell Identification (CCSI) test and the Seoul Neuropsychological Screening Battery. Additionally, the additive effects of concurrent WMH and olfactory dysfunction on cognitive performance were investigated using binary logistic regression.
Results: The deep WMH score exhibited a significant negative correlation with the CCSI score ($p = 0.026$) but the total WMH and periventricular WMH did not. A multiple regression analysis revealed that the total WMH ($\beta = -0.109$, $p = 0.011$) and deep WMH ($\beta = -0.153$, $p = 0.020$) severities had significant negative correlations with semantic fluency. A logistic regression analysis revealed that the simultaneous presence of severe olfactory dysfunction and deep WMH was associated with a greater risk for the semantic fluency impairments (odds ratio = 15.909, $p = 0.0005$) compared to patients with mild deep WMH or high CCSI scores.
Conclusions: These data indicate that deep WMH was closely coupled with olfactory impairments and cognitive decline in PD. Moreover, the concurrent presence of severe deep WMH and olfactory impairments has a greater influence on semantic fluency.

1. Introduction

The olfactory dysfunction occurs in early stages of clinical Parkinson's disease and in asymptomatic relative of PD patient with a prevalence of approximately 90% [1]. As the olfactory system is one of induction sites for α-synuclein, neurodegenerative changes in this system occur early in the course of PD [2,3]. Importantly, recent studies have demonstrated a close association between olfactory dysfunction and cognitive status as well as ongoing cognitive decline in patients with PD [4]. Therefore, olfactory performance in the early stage of PD seems to play an important role in modulation of PD-related cognitive performance.

Previous studies have shown that microstructural or gross abnormality around white matter regions of olfactory system appear to negatively influence on olfactory performance in several disease entities, including idiopathic hyposmic subjects [5], and mild cognitive impairment (MCI) [6]. Similarly, microstructural alterations in the white matter of the central olfactory system that are associated with impaired olfaction are present in early stage PD patients [7]. Additionally, the burden of white matter hyperintensities (WMH) is a major contributor to the development of

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dementia in patients with PD-MCI [8]. These studies suggest that the concurrent presence of white matter pathologies and olfactory dysfunction may have a negative additive impact on cognitive performance in patients with PD.

Based on magnetic resonance imaging (MRI) scans, WMH may be categorized as deep WMH (DWMH), or patchy areas of WMH in subcortical white matter, and periventricular WMH (PWMH), which are adjacent to the cerebral ventricles [9]. These WMH subtypes exhibit different neuropathologies [10] and etiological mechanisms [9,11]. Thus, the present study investigated the effects of WMH on olfactory dysfunction and cognitive impairments according to WMH type in patients with non-demented PD. Additionally, this study evaluated whether the concurrent presence of WMH and olfactory dysfunction has an additive influence on cognitive performance by analyzing neuropsychological test data according to WMH severity and the degree of olfactory dysfunction.

2. Patients and methods

2.1. Subjects

The present study was retrospective and utilized 171 patients with non-demented PD who were recruited from a university hospital between January 2008 and January 2013. Of patients enrolled in this study, 54 and 35 patients participated in our previous studies dealing with olfaction and white matter hyperintensities in PD [2,8], respectively, and 23 patients participated in both previous studies. PD was diagnosed according to the clinical diagnostic criteria of the United Kingdom PD Society Brain Bank and odor identification was assessed with the Cross-Cultural Smell Identification (CCSI) test [12]. Additionally, only patients who displayed decreased dopamine transporter uptake in the posterior putamen on a [18F] FP-CIT positron emission tomography (PET) scan were included in this study.

The neuropsychological performance was evaluated using standardized neuropsychological test, Seoul Neuropsychological Screening Battery (SNSB) [13]. The SNSB measures attention, language, visuoconstructive function, verbal and visual memory, and frontal/executive function. Each of these quantifiable cognitive tests has age-, sex-, and education-specific norms available that are based on 447 normal subjects. All patients had scores on the Korean version of the Mini-mental State Examination (K-MMSE) above the 16th percentile for their age- and education-appropriate norms. Additionally, the patients did not exhibit evidence of cognitive dysfunction-related changes in activities of daily living (ADL).

Parkinsonian motor symptoms were assessed using the Unified PD Rating Scale Part III (UPDRS-III) and basic demographic data regarding gender, age, and histories of hypertension, diabetes mellitus, cerebrovascular accidents, or ischemic heart disease were also collected. The exclusion criteria consisted of evidence of focal brain lesions on the MRI scans or the presence of other neurodegenerative diseases that might account for cognitive and olfactory dysfunction. In addition, 36 healthy age- and sex-matched controls were selected from medical records, who had completed brain MRI scan and neuropsychological assessment. This study was approved by the Institutional Review Board of Yonsei University Severance Hospital. Written informed consent was obtained from all subjects participating in this study.

2.2. Brain MRI

All MRI scans of the PD patients were acquired using a 3.0-T system (Intera or Achieva; Philips Medical System; Best, The Netherlands) and WMH were determined using fluid attenuated inversion recovery sequence (FLAIR) images (TR/TE/TI, 8502/132/2100 ms, 5-mm section thickness). The WMH scores were rated using a semi-quantitative visual rating system [14], which provides four sum scores in a semi-quantitative manner: PWMH (0–6), DWMH (0–24), basal ganglia WMH (0–30), and infratentorial WMH (0–24). The WMH scores were rated blindly (by HJH and SMK) and the intra- and inter-scorer reliability scores (expressed as correlation coefficients) were 0.93 and 0.86, respectively.

2.3. Statistical analysis

Differences in the baseline demographic characteristics between PD patients and normal control were evaluated using an analysis of variance test for continuous variables or the chi-Square test for categorical variables. An analysis of covariance (ANCOVA) was used to compare differences between PD patients and normal control for the neuropsychological testing, and it was adjusted for age, gender, education level, and K-MMSE scores. Multiple regression analyses were performed to investigate the effects of WMH on olfactory dysfunction and cognitive performance. In the multiple regression analysis for olfactory performance, age, gender, disease duration, and WMH scores were used as independent variables and the CCSI score was the dependent variable. In a multiple regression analysis for cognitive performance, age, gender, education duration, K-MMSE, and WMH scores were used as independent variables and the cognitive subsets were the dependent variables. Additionally, to evaluate additive effects of WMH severity and the degree of olfactory dysfunction on cognitive function, a binary logistic regression analysis was performed. Of the various WMH and cognitive subset types, DWMH and semantic fluency were chosen because these variables survived in the correlation analyses that were conducted to evaluate WMH severity and olfactory or cognitive performance.

Next, the patients were divided into two groups according to the severity of DWMH, CCSI score, and semantic fluency. Based on DWMH score, PD patients were categorized into high-grade (>10, n = 18) and low-grade (0–10, n = 153) DWMH groups. Based on CCSI score, PD patients were categorized into low (0–4, n = 32) and high (5–12, n = 139) CCSI groups. Based on semantic fluency, the patients were categorized into low (<16th percentile, n = 30) and high (≥16th percentile, n = 141) semantic fluency groups. Finally, the patients were reclassified into four subgroups according to the severity of DWMH and CCSI score (Supplementary Fig. 1): patients with low-grade DWHM and high CCSI (subgroup A, n = 116), patients with low-grade DWHM and low CCSI (subgroup B, n = 37), patients with high-grade DWHM and high CCSI (subgroup C, n = 10), and patients with high-grade DWHM and low CCSI group (subgroup D, n = 8). In the binary logistic regression analysis used to assess cognitive function, these subgroups were used as independent variables and the groups categorized based on semantic fluency were used as dependent variables. Subgroup A was designated the reference group. Additionally, to confirm the general propensity of semantic fluency function according to DWMH severity and olfactory function, we performed sensitivity analysis after changing the number of subgroups. Moreover, we applied the receiver operating characteristic (ROC) analysis to determine optimal cut-off values of the severity of DWMH and CCSI score with the Youden's index (sensitivity + specificity-1). After selecting maximum value of the index as the optimum cut-off point, the subgroups were reclassified for the binary logistic regression analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc.; Chicago, IL, USA), and a p value <0.05 was considered to indicate significance.