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Volumetric analysis of the substantia innominata in patients with Parkinson's disease according to cognitive status

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Abstract

The cholinergic system arising from the substantia innominata (SI) of the basal forebrain has an important role in the cognitive functions of Parkinson's disease (PD). We performed magnetic resonance imaging based volumetric analysis to evaluate the SI volume in patients with PD-intact cognition (PD-IC), PD-mild cognitive impairment (PD-MCI), and PD dementia (PDD). The mean normalized SI volume was significantly decreased in patients with PD-IC (1.54 ± 0.12, $p < 0.001$), PD-MCI (1.49 ± 0.12, $p < 0.001$), and PDD (1.39 ± 0.12, $p < 0.001$) compared with that of control subjects (1.68 ± 0.11). The normalized SI volume did not differ between patients with PD-IC and PD-MCI; however, the normalized SI volume was significantly decreased in patients with PDD compared with that in those with PD-IC ($p < 0.001$) or PD-MCI ($p = 0.016$). The normalized SI volume was significantly correlated with general cognitive status ($r = 0.51$, $p < 0.001$) as well as with performance in each cognitive subdomain, with a particularly significant independent association with attention ($\beta = 0.33$, $p = 0.003$) and object naming ($\beta = 0.26$, $p = 0.017$). The present study demonstrated that the SI volume in PD differs depending on cognitive status and is significantly correlated with cognitive performance.

Keywords: Parkinson's disease; Substantia innominata; Mild cognitive impairment; Dementia

1. Introduction

The key feature of cognitive profiles in Parkinson's disease (PD) is executive dysfunction that has difficulty in tasks that require generation of mental sets, planning, and cognitive sequencing. Patients with PD with dementia (PDD) often exhibit poorer performance in visuospatial tasks, retrieval deficit in memory tasks, and decreased verbal fluency (Caballol et al., 2007). The prevalence of PDD varies widely, with recent studies indicating a range of 19%–78% (Biggins et al., 1992; de Lau et al., 2005; Hobson and Meara, 2004; Levy et al., 2002). Recently, several studies have demonstrated that substantial portions of patients with PD have quantifiable cognitive dysfunctions that do not meet dementia criteria, and this form of dysfunction has been defined as mild cognitive impairment (MCI) (Caviness et al., 2007; Janvin et al., 2006). As in Alzheimer's disease (AD), patients with PD-MCI have a higher risk of developing dementia (Janvin et al., 2006). A recent epidemiological study showed that about 19% of patients with untreated early PD were classified as MCI (Aarsland et al., 2009).

Although a neural basis for cognitive dysfunctions in PD remains unknown, pathological and functional neuroimaging studies suggest that the cholinergic system arising from the basal forebrain has an important role in cognitive functions of PD patients. A recent positron emission tomography (PET) study using in vivo imaging of cerebral acetyl-

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cholinesterase demonstrated that cholinergic dysfunction occurs even in the early course of PD and is more widespread and profound in PDD (Hilker et al., 2005; Shimada et al., 2009). Braak et al. (2003), in a staging study of PD pathology, also noted that basal forebrain pathology occurs simultaneously with nigral pathology.

The nucleus basalis of Meynert located in the substantia innominata (SI) of the basal forebrain is the major source of cholinergic input to the cerebral cortex, and degeneration of the basal forebrain may represent decline of cholinergic activity in the cerebral cortex (Bohnen and Albin, 2010). A few imaging studies of the SI in patients with PD have reported evidence of SI atrophy or a significant correlation between SI thickness and general cognition (Hanyu et al., 2002; Oikawa et al., 2004). However, previous studies measured length rather than volume, and the number of patients with PDD was very limited, and PD subgroups were not delineated according to cognitive status. In the present study, we directly compared the SI volume of PD-intact cognition (PD-IC), PD-MCI, and PDD subgroups using magnetic resonance imaging based volumetric analysis to evaluate the structural status of basal forebrain atrophy according to cognitive status in patients with PD. In addition, we also analyzed correlations between SI volume and performance on individual tests of cognitive subdomains.

2. Methods

2.1. Subjects

We prospectively enrolled 24 patients with PD-IC, 35 with PD-MCI, and 29 with PDD from a university hospital. PD was diagnosed according to the clinical diagnostic criteria of the UK PD society Brain Bank (Hughes et al., 1992). Information concerning memory problems and other subjective cognitive deficits was obtained using a care giver-based interview. To determine cognitive subsets in the diagnosis of PD-MCI or PDD, we used the Seoul Neuropsychological Screening Battery (SNSB) (Kang and Na, 2003; Lee et al., 2010). The Seoul Neuropsychological Screening Battery (SNSB) covers attention, language, praxis, 4 elements of Gerstmann syndrome, visuoconstructive function, verbal and visual memory, and frontal/executive function. Among these, the quantifiable tests comprised the digit span (forward and backward), the Korean version of the Boston Naming Test (K-BNT; Kim and Na, 1999), the Rey Complex Figure Test (RCFT); copying, immediate and 20-minute delayed recall, and recognition), Seoul Verbal Learning Test (SVLT); 3 learning-free recall trials of 12 words, 20-minute delayed recall trial for these 12 items, and a recognition test), phonemic and semantic Controlled Oral Word Association Test (COWAT), and Stroop test (word and color reading of 112 items during a 2-minute period). Age-, sex-, and education-specific norms for each test based on 447 normal subjects are available (Kang and Na, 2003). The scores of these quantifiable cognitive tests were classified as abnormal when they were below the sixteenth percentiles of the norms for the age-, sex-, and education-matched normal subjects.

PD-IC was defined if there were no objective cognitive dysfunctions. Along with concept of MCI suggested by Petersen and colleagues (1999), the diagnosis of MCI in patients with PD was made if at least 1 of 5 cognitive domains was abnormal. All PD-MCI patients had scores of Korean version of Mini Mental State Examination (MMSE) (K-MMSE) above the sixteenth percentile for age and educational appropriate norm, and also showed no evidence of abnormal activities of daily living. PDD was diagnosed according to clinical diagnostic criteria for probable PDD (Emre et al., 2007). Parkinsonian motor symptoms were assessed using the Unified PD Rating Scale Part III (UPDRS-III). Patients having history of offending drugs causing parkinsonism (antipsychotics, gastrointestinal kinetics, antiepileptic drugs, or L-type calcium channel blockers) were excluded.

Exclusion criteria included evidence of focal brain lesions by MRI or the presence of other neurodegenerative diseases that might account for dementia. Possible medical comorbidities were also excluded by laboratory tests, including thyroid function test, vitamin B12 and folic acid levels, and a VDRL test. Healthy age- and gender-matched elderly volunteers were used as controls for MRI-based volumetric analysis. They were recruited by advertisements about the project, or were healthy relatives of patients with movement disorders or dementia ($n = 28$, age = 70.5 year). The controls had no active neurological disorders, no cognitive complaints, and normal performance on the neuropsychological tests with a minimum score of 28 on the K-MMSE. Informed consent was obtained from all patients and control subjects. This study was approved by the Institutional Review Board of our hospital.

2.2. MRI acquisition

All scans of healthy controls and patients with PD-IC, PD-MCI, and PDD were acquired using a Philips 3.0-T scanner (Philips Intera; Philips Medical System, Best, The Netherlands) with a SENSE head coil (SENSE factor = 2). Head motion was minimized with restraining foam pads provided by the manufacturer. A high-resolution T1-weighted MRI volume data set was obtained from all subjects using 3D T1-TFE sequence configured with the following acquisition parameters: axial acquisition with a 224 × 256 matrix; 256 × 256 reconstructed matrix with 182 slices in the coronal plane; 1-mm-thick sections; 220-mm field of view; 0.98 × 0.98 × 1.2 mm^3 voxels; TE, 4.6 ms; TR, 9.6 ms; flip angle, 8°; slice gap, 0 mm.

2.3. Volumetric determination of SI

The volumes of the SI were determined by manually delineating the boundaries of this structure with MRIcro software (Rorden and Brett, 2000) on the coronal T1-