Analysis of the Substantia Innominata Volume in Patients with Parkinson's Disease with Dementia, Dementia with Lewy Bodies, and Alzheimer's Disease

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Background and Purpose: The substantia innominata (SI) contains the nucleus basalis of Meynert, which is the major source of cholinergic input to the cerebral cortex. We hypothesized that degeneration of the SI and its relationship to general cognitive performance differs in amyloidopathy and synucleinopathy. **Methods:** We used magnetic resonance imaging (MRI)-based volumetric analysis to evaluate the SI volume in patients with amnestic mild cognitive impairment (aMCI), Alzheimer's disease (AD), Parkinson's disease-mild cognitive impairment (PD-MCI), PD with dementia (PDD), dementia with Lewy bodies (DLB), and healthy elderly controls. The correlation between SI volume and general cognitive performance, measured using the Korean version of the Mini-Mental State Examination (K-MMSE), was examined. **Results:** Compared to control subjects, the mean normalized SI volume was significantly decreased in all of the other groups. The normalized SI volume did not differ between the subjects with PDD and DLB, whereas it was significantly smaller in subjects with PDD ($p = 0.029$) and DLB ($p = 0.011$) compared with AD. In subjects with PD-related cognitive impairment (PD-MCI, PDD, or DLB), there was a significant positive correlation between the SI volume and K-MMSE score ($r = 0.366$, $p < 0.001$), whereas no correlation was seen in subjects with AD-related cognitive impairment (aMCI or AD). **Conclusions:** Our data suggest that the SI loss is greater in synucleinopathy-related dementia (PDD or DLB) than in AD and that the contribution of the SI to cognitive performance is greater in synucleinopathy than in amyloidopathy.

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The substantia innominata (SI) contains the nucleus basalis of Meynert, which is the major source of cholinergic input to the cerebral cortex. There is ample evidence that SI volume loss has an important role in cognitive decline in various neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) with dementia (PDD), and dementia with Lewy bodies (DLB).[1,2] In patients with AD, studies have demonstrated that the accumulation of beta amyloid and neurofibrillary tangles leads to significant neuronal loss in the nucleus basalis.[3,4] Additionally, functional image studies that measured acetylcholinesterase activity in the brain using positron emission tomography (PET) and radiolabeled acetylcholine analogues N-[^{11}C]-methyl-4-piperidyl propionate (MP4P) have revealed a loss of choline acetyltransferase activity in subjects with AD.[5] Degeneration of the SI is also seen in alpha-synucleinopathy-related neurodegenerative disease, such as PDD or DLB.[6] In a staging study of PD pathology, Braak et al.[7] reported that basal forebrain pathology occurs simultaneously with nigral pathology, and the pathological change in the SI occurs early in PD. *In vivo* functional imaging studies using PET with MP4P showed that the brain cholinergic deficit begins in early PD and is more widespread and profound in both PDD and DLB.[8,9]

Despite the cholinergic role in both AD- and PD-related dementia, the degree of the cholinergic contribution seems to differ among the dementia subgroups. Pathology data have revealed that the neuronal loss in the nucleus basalis of Meynert was more prominent in pa-

tients with DLB compared to those with AD.[6,10,11] Several imaging studies support the pathology data; the thickness of the SI was decreased significantly in patients with DLB compared with those with AD[12,13] and the loss of cortical cholinergic activity was more severe in patients with PDD or DLB compared with those with AD.[14]

The degree of SI atrophy is important clinically, as this affects the response to cholinergic drugs. The change in the Mini-Mental State Examination (MMSE) score after administering a cholinesterase inhibitor was inversely and significantly correlated with the thickness of the SI in patients with AD and DLB, implying that the clinical response to cholinergic therapy is partly attributable to damaged cholinergic neurons.[13,15] Several studies have reported evidence of the SI atrophy or a significant correlation between SI thickness and general cognition.[2,16]

However, measuring volume rather than length reflects the degree of atrophy more precisely. In this study, to evaluate the structural status of basal forebrain atrophy in various types of dementia, we directly compared the SI volume in PD- and AD-related cognitive dysfunction, including mild cognitive impairment (MCI), using magnetic resonance imaging (MRI)-based volumetric analysis. Additionally, we analyzed the correlations between SI volume and general cognitive status in AD- and PD-related cognitive dysfunctions.

Methods

Subjects

We retrospectively enrolled 24 cognitively normal subjects, 45 patients with amnestic mild cognitive impairment (aMCI), 40 with AD, 38 with Parkinson's disease-mild cognitive impairment (PD-MCI), 31 with PDD, and 22 with DLB from patients seen in the movement disorders and dementia outpatient clinic at a university hospital. Information on the patients' cognitive deficits was obtained from a caregiver-based interview. To determine cognitive subsets in the diagnosis of MCI or dementia type, we used the Seoul Neuropsychological Screening Battery (SNSB).[17] The SNSB covers attention, language, praxis, four elements of Gerstmann syndrome, visuoconstructive function, verbal and visual memory, and frontal/executive function. The quantifiable tests used were the digit span (forward and backward), the Korean version of the Boston Naming Test,[18] the Rey Complex Figure Test (copying, immediate and 20-minute delayed recall, and recognition), the Seoul Verbal Learning Test (three learning-free recall trials of 12 words, 20-minute delayed recall trial for these 12 items, and a recognition test), the phonemic and semantic Controlled Oral Word Association Test, and the 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.[17] 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.

A patient was diagnosed with aMCI when at least one of the five cognitive domains, including the memory domain, was abnormal, and the patient did not meet the criteria for dementia. Using the concept of MCI suggested by Petersen et al.[19] the diagnosis of MCI in patients with PD was made if at least one of the five cognitive domains was abnormal. All the aMCI and PD-MCI patients had scores on the Korean version of the MMSE (K-MMSE) above the sixteenth percentile for the age- and educational-appropriate norm and showed no evidence of deficits in activities of daily living.

The clinical diagnosis of probable AD followed the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association guidelines.[20] Patients were assigned to PDD when dementia occurred in the context of well-established PD (according to the UK Parkinson Disease Society Brain Bank criteria) with a time interval of at least 1 year after the onset of the motor syndrome.[21,22] Probable DLB was diagnosed according to the consensus guidelines of the third report of the DLB Consortium.[23]

Exclusion criteria were evidence of focal brain lesions, diffuse white matter hyperintensities, or multiple lacunae in the basal ganglia on MRI. Possible medical comorbidities were excluded by laboratory tests, including thyroid function tests, vitamin B_{12} and folic acid levels, and the VDRL test. Healthy age- and gender-matched elderly volunteers were used as controls for the MRI-based volumetric analysis. They were recruited by advertisements about the project or were healthy relatives of patients with movement disorders or dementia ($n = 24$, age = 72.0 years).

MRI acquisition

All scans of healthy controls and patients with AD, PDD, and DLB 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 using restraining foam pads provided by the manufacturer. A high-resolution T1-weighted MRI volume dataset was obtained for all subjects using the 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 mm³ voxels; TE, 4.6 ms; TR, 9.6 ms; flip angle, 8°; slice gap, 0 mm.

Volumetric determination of SI

The delineation of the SI on MRI was based on the method reported by George et al.[1] The SI volume was measured on three consecutive coronal sections using the following de-

marcation. For the first section at the level of the crossing of the anterior commissure, the ventral aspect of the globus pallidus demarcated the dorsal border of the SI, and the ventral border was the base of the brain containing the anterior perforated space. The medial border of the SI was defined by a vertical line extending from the ventrolateral border of the bed nucleus of the brain. The lateral border extended to the medial aspect of the putamen. The second section was between the first and third sections, and the third section was at the level of the emergence of the anterior commissure from the temporal lobe. To correct for individual brain size, the volumes were normalized by dividing by the total intracranial volume derived from sagittally formatted 10-mm slices. The normalized SI volume was defined by the following formula: total SI volume (mm^3)/total intracranial volume (mm^3) $\times$ 10,000. The intra- and inter-rater reliability were 0.82 and 0.80, respectively.

Statistical analysis

Data are expressed as the mean $\pm$ standard deviation. One-way analysis of variance followed by post hoc comparisons was used to compare group differences in age, duration of education, total intracranial volume, normalized SI volume, and the K-MMSE and Clinical Dementia Rating scores. The chi-square test was used to compare the gender distribution. Pearson's correlation analysis was used to analyze the relationship between SI volume and the K-MMSE score. Statistical analysis was performed using SPSS ver. 17.0, and p-values < 0.05 were considered significant.

Results

Demographic characteristics

The demographic characteristics of the patients are shown in Table 1. No significant difference in age, gender, education level, or total intracranial volume was found among the control, aMCI, PD-MCI, AD, PDD, and DLB groups.
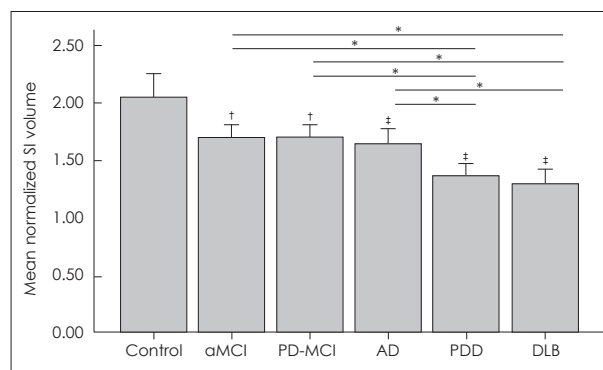
Comparison of SI volume among groups

Compared with the control subjects (2.05 $\pm$ 0.52), the mean normalized SI volume was significantly smaller in the patients with aMCI (1.70 $\pm$ 0.39, p = 0.006), PD-MCI (1.70 $\pm$ 0.35, p = 0.008), AD (1.65 $\pm$ 0.41, p < 0.001), PDD (1.36 $\pm$ 0.32, p < 0.001), and DLB (1.30 $\pm$ 0.33, p < 0.001). Compared with the patients with aMCI, the normalized SI volume was significantly smaller in the patients with PDD (p = 0.003) and DLB (p = 0.001); however, the volume did not differ significantly from those with AD. Compared with the patients with PD-MCI, the normalized SI volume was significantly smaller in the patients with PDD (p = 0.003) and DLB (p = 0.001). On

Figure 1. The mean normalized substantia innominata (SI) volume among groups. The degree of atrophy of the SI was in the order control < (aMCI, PD-MCI, AD) < (PDD, DLB). Compared with the controls, the mean normalized SI volume was significantly smaller in patients with aMCI, PD-MCI, AD, PDD, and DLB. Compared with aMCI subjects, the normalized SI volume was significantly smaller in patients with PDD and DLB. Compared with PD-MCI subjects, the normalized SI volume was significantly smaller in patients with PDD and DLB. On comparing the dementia subjects, the normalized SI volume did not differ between patients with PDD and those with DLB, whereas the normalized SI volume was significantly smaller in subjects with PDD and DLB compared with the AD subjects. Error bars indicate the standard error. *p < 0.05, †p < 0.05 compared with the controls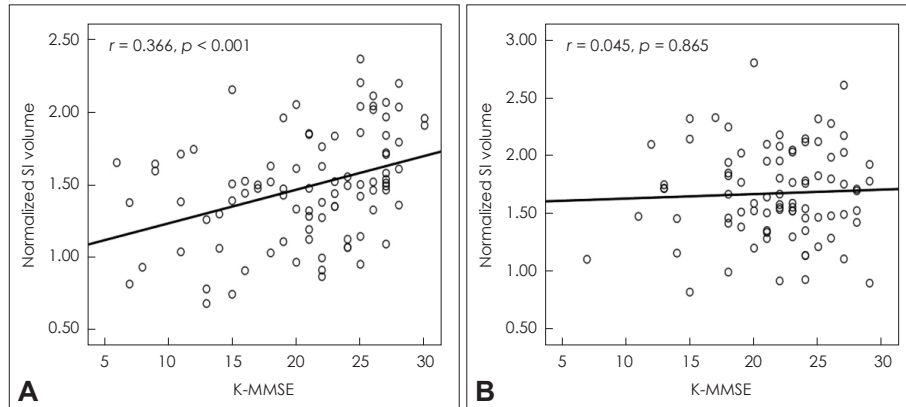, ‡p < 0.001 compared with the controls. aMCI: amnestic mild cognitive impairment, PD-MCI: Parkinson's disease-mild cognitive impairment, AD: Alzheimer's disease, PDD: Parkinson's disease with dementia, DLB: dementia with Lewy bodies.

Table 1. Demographic characteristics of the groups

	Control	aMCI	PD-MCI	AD	PDD	DLB	p value
Participants (n)	24	45	38	40	31	22	
Age (years)	72.0 (2.8)	73.53 (5.0)	72.9 (5.1)	74.4 (7.9)	71.4 (6.6)	75.1 (5.9)	NS
Number of males	6	18	22	19	14	8	NS
Education duration (years)	9.9 (5.7)	9.3 (5.3)	9.7 (4.8)	9.3 (6.4)	6.5 (6.0)	8.5 (5.9)	NS
Total intracranial volume (mm^3)	1,306,483 (141,892)	1,327,652 (101,015)	1,356,437 (124,898)	1,296,226 (125,077)	1,319,263 (132,731)	1,316,686 (101,325)	NS
Normalized SI volume	2.05 (0.52)	1.70 (0.39)	1.70 (0.35)	1.65 (0.41)	1.36 (0.32)	0.30 (0.33)	<0.001
K-MMSE score	26.5 (2.7)	24.2 (3.2)	25.6 (2.5)	18.9 (4.4)	18.7 (4.8)	15.8 (5.8)	<0.001
CDR	0.4 (0.2)	0.5 (0.0)	0.5 (0.0)	1.0 (0.3)	1.1 (0.5)	1.6 (0.9)	<0.001

aMCI: amnestic mild cognitive impairment, PD-MCI: Parkinson's disease-mild cognitive impairment, AD: Alzheimer's disease, PDD: Parkinson's disease with dementia, DLB: dementia with Lewy bodies, SI: substantia innominata, CDR: Clinical Dementia Rating, K-MMSE: Korean version of the Mini-Mental State Examination, NS: not significant.

Figure 2. The relationship between the normalized substantia innominata (SI) volume and the score on the Korean version of the Mini-Mental State Examination (K-MMSE). A: In subjects with PD-related cognitive impairment (PD-MCI, PDD, or DLB), there was a significant positive correlation between the SI volume and K-MMSE score (r = 0.366, p < 0.001). B: By contrast, in patients with AD-related cognitive impairment (aMCI or AD), there was no significant correlation between the SI volume and K-MMSE score (r = 0.045, p = 0.685). aMCI: amnestic mild cognitive impairment, PD-MCI: Parkinson's disease-mild cognitive impairment, AD: Alzheimer's disease, PDD: Parkinson's disease with dementia, DLB: dementia with Lewy bodies.

comparison among dementia subjects, the normalized SI volume did not differ between patients with PDD and DLB. However, the normalized SI volume was significantly decreased in subjects with PDD (p = 0.029) and DLB (p = 0.011) compared with AD subjects (Figure 1).

Correlation analysis of SI volume and general cognition

In patients with AD-related cognitive impairment (aMCI or AD), there was no significant correlation between the SI volume and general cognitive function, as measured using the K-MMSE score (r = 0.045, p = 0.685) (Figure 2B). In contrast, the SI volume in subjects with PD-related cognitive impairment (PD-MCI, PDD, or DLB) showed a significant positive correlation with general cognitive function (r = 0.366, p < 0.001) (Figure 2A).

Discussion

This study evaluated whether degeneration of the SI and its relationship to general cognitive performance differ in AD- and PD-related cognitive impairments. The major findings of this study were 1) the mean normalized SI volume was significantly smaller in patients with either aMCI or PD-MCI, 2) the loss of SI volume was greater in PD-related dementia (PDD or DLB) than in AD, and 3) SI volume was significantly correlated with general cognitive decline only in patients with PDD or DLB.

A few studies have examined SI volume using MRI in patients with MCI; however, the results are conflicting. Muth et al.[24] and Grothe et al.[25] reported that the SI volume was significantly decreased in MCI compared with normal elderly controls, whereas George et al.[1] showed that the SI volume in MCI did not differ from that in controls. In patients with PD,

we previously reported that the SI volume was significantly decreased in PD-MCI compared with the controls.[26] In the present study, we found that the SI volume was significantly decreased in aMCI and PD-MCI, suggesting that cholinergic degeneration occurs with MCI status regardless of the AD or PD prototypes.

Studies that compared the SI atrophy in AD and DLB by measuring the SI length[12,13] have shown that the thickness of the SI was significantly greater in AD than in DLB, which concurs with our SI volume analysis. However, no previous reports have compared the SI atrophy between PDD and AD. Our data showed that the normalized SI volume was significantly smaller not only in subjects with DLB but also in subjects with PDD compared with AD. Because a study showed that cortical cholinergic activity is more severely affected in parkinsonian dementia than in Alzheimer disease,[14] our result suggests that the degeneration of the cholinergic system arising from the nucleus basalis of Meynert is more closely coupled with PD-related dementia than with AD-related dementia. On comparing subjects with alpha-synuclein-related dementia, the normalized SI volume did not differ between patients with PDD and DLB. This result is in line with a functional PET imaging study that showed that the cholinergic activity did not differ between PDD and DLB.[8] Accordingly, previous data and ours support the concept that PDD and DLB lie on a common disease spectrum with respect to cholinergic pathophysiology.

Contrary to previous reports,[1] in the subjects with AD-related cognitive impairment (aMCI or AD), there was no significant correlation between the SI volume and general cognitive function. In contrast, there was a significant positive correlation between the SI volume and general cognitive function in the subjects with PD-related cognitive impairment (PD-MCI, PDD, or DLB). This suggests that cognitive performance is

closely dependent on the cholinergic system in PD-related cognitive impairment, whereas this relationship is weak in AD-related cognitive impairment. Furthermore, this finding in our study is supported by a previous clinical study indicating that the response to cholinesterase inhibitors is greater in DLB than in AD.[27-29]

In summary, our data suggest that the SI volume loss is greater in alpha-synucleinopathy-related dementia (PDD or DLB) than in AD, and the contribution of the SI to cognitive performance is greater in alpha-synucleinopathy-related cognitive impairments than in AD.

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