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Subcortical whiter matter hyperintensities within the cholinergic pathways of patients with dementia and parkinsonism

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ABSTRACT

Background and purpose: White matter hyperintensities (WMHs) in the cholinergic pathways are associated with cognitive performance in Alzheimer's disease (AD) and Parkinson disease dementia (PDD). This study aimed to evaluate the relationship between loss of white matter cholinergic pathways and cognitive function in patients with AD, diffuse Lewy body disease (DLB), and PDD.
Methods: The subjects included 20 patients with AD, 17 with DLB, 21 with PDD, and 20 healthy controls. The extent of WMHs within cholinergic pathways was assessed using the Cholinergic Pathways Hyperintensities Scale (CHIPS) and was compared among the different diseases.
Results: The mean CHIPS scores were similar among the three dementia groups (AD vs. DLB vs. PDD = 34.6 ± 17.9 vs. 32.4 ± 14.1 vs. 31.8 ± 14.5, $p = 0.781$ by ANCOVA) and higher than those of controls (11.5 ± 7.6, $p = 0.001$ by ANCOVA).
Conclusions: Losses of cholinergic pathways were similar among AD, DLB, and PDD groups, and more severe cognitive dysfunction was associated with elevated WMHs. These findings suggest that interruption of acetylcholine pathways may be related to cognitive dysfunction in these three diseases, even though they have different pathological mechanisms.

1. Introduction

Cerebral white matter hyperintensities (WMHs) on magnetic resonance imaging (MRI) are frequent findings in elderly people with or without dementia and are associated with vascular risk factors, such as increasing age and hypertension [1,2]. Increasing WMHs are correlated with cognitive dysfunction [3]. Association does not imply causation; however, it is possible that white matter changes can interrupt subcortico-cortical neurotransmitter pathway projections [4]. Such damage to cholinergic pathways projecting from the nucleus basalis to almost every part of the cerebral cortex is associated with cognitive decline.

The Cholinergic Pathways Hyperintensities Scale (CHIPS) is spatially associated with white matter changes in cholinergic pathways. This methodology can visually assess the degree of WMH load on selected MRI slices located in specific anatomical structures containing cholinergic tracts [5]. Previous studies have shown that CHIPS score was associated with Alzheimer's disease (AD), vascular dementia, Parkinson's disease dementia (PDD), and PD-mild cognitive impairment (PD-MCI) [6,7].

Parkinsonism and dementia are umbrella terms that refer to a spectrum of illnesses including AD, DLB, and PDD. These may be mutually exclusive disorders given the separate nature of the initial clinical symptoms, the preferential localization of the fundamental pathology, and the differing genetic linkages; however, clinically and pathologically, there is striking overlap among these syndromes. Pathological features, such as amyloid plaques, a hallmark of Alzheimer's, are also commonly observed in patients with DLB and PDD [8,9]. Pathological overlap among AD, DLB, and PDD gives rise to various clinical admixtures of dementia and parkinsonism. The clinical relevance of cholinergic pathways in this spectrum of disease is uncertain.

The hypothesis of this study is that the severities of WMH within cholinergic pathways are different among the spectrum of dementia and parkinsonism disorders. We investigated how the CHIPS burden differed in patients with AD, DLB, and PDD. In addition, we analyzed the correlation between the CHIPS score and each cognitive subdomain in this spectrum of cognitive disorders.

2. Methods

2.1. Patients

The study was approved by the ethics committee of Seoul St. Mary's Hospital. Each patient gave written informed consent before participating.

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A total of 58 newly diagnosed patients at the Department of Neurology of Seoul St. Mary's Hospital were enrolled in this study from January 2013 to December 2013. Patients were recruited using clinical diagnostic criteria for AD, DLB, and PDD [10–12]. Twenty healthy elderly subjects, free from any neurological or psychiatric history, were enlisted to serve as controls. Patient information was obtained, including age; sex; education; disease duration; history of hypertension, diabetes mellitus, or dyslipidemia; and smoking status. Laboratory tests that could affect cognitive function, including homocysteine, vitamin B12, and folate were performed for all subjects, and thyroid, hepatic, and renal functions were assessed. Those with abnormalities were excluded. Patients with PDD and DLB were evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) part I to part III and classified by modified Hoehn and Yahr (H&Y) stage. Myocardial ^{123}I-metaiodobenzylguanidine scintigraphy was performed in all patients, and positron emission tomography using ^{18}F-N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane was performed in selected patients to differentiate the conditions.

All patients with AD had intact cardiac sympathetic innervation and normal dopamine transporter uptake, whereas PDD and DLB showed was characterized by cardiac sympathetic denervation and defective dopamine transporter uptake.

2.2. Neuropsychological tests

Information about memory problems and other subjective cognitive deficits was obtained from caregiver interviews. General cognitive status and dementia severity were evaluated using the Korean version of the Mini-Mental Status Examination, the Clinical Dementia Rating scale, and the "sum of the box" of the Clinical Dementia Rating scale. To assess cognitive domains, we used the Seoul Neuropsychological Screening Battery [13], which assesses attention, language, praxis, four elements of Gerstmann syndrome, visuospatial function, verbal and visual memory, and frontal/executive function. Quantifiable indices included the forward and backward digit span tasks; the Korean version of the Boston Naming Test; the Rey–Osterrieth Complex Figure Copy; the Seoul Verbal Learning Test for verbal memory; the Rey–Osterrieth Complex Figure Test for nonverbal, visuospatial memory; the Controlled Oral Word Association Test (semantic: animals and grocery items, phonemic: Korean letters) for word fluency; and the Stroop color/word conflict test. Frontal motor functions were assessed by motor impersistence, contrasting program, go–no go test, fist–edge–palm, alternating hand movement, alternating square and triangle, and Luria loop tests. Test scores were classified as abnormal when they were <16% of the scores of age-, sex-, and education-matched normal subjects [13]. Frontal motor function was considered "abnormal" if more than two of seven tests showed abnormalities.

2.3. MRI and CHIPS scale

All patients underwent 3.0-Tesla MRI (Magnetom Verio, 3T, Siemens). White matter hyperintensities were quantified on axial sections of fluid-attenuated inversion recovery sequence images using the recently developed visual rating scale CHIPS [5–7], which quantifies the extent of WMH in the periventricular and subcortical white matter.

2.4. Data analysis and statistics

Statistical analysis was performed with SPSS software version 15.0. Independent means t-tests or one-way ANOVAs (with Bonferroni post-hoc testing) were used to compare groups, and Chi-square tests were used to compare frequencies for categorical variables. Each neuropsychological test result and CHIPS score was analyzed with analysis of covariance (ANCOVA) including a priori confounders. Spearman correlation coefficients were used to compute the associations between CHIPS score and cognitive tests. Statistical significance was defined as $P < 0.05$.

3. Results

Among the 58 patients studied (16 males and 42 females; mean age ± SD, 76.8 ± 7.1 years; mean disease duration, 2.5 ± 1.8 years; mean education duration, 7.9 ± 5.3 years), 20 had AD, 17 had DLB, and 21 had PDD.

The groups were similar in terms of gender distribution, disease duration, level of education, and presence of hypertension, diabetes mellitus, and cigarette smoking (Table 1). Mean age was higher in all dementia patients than in controls. Comparison of UPDRS and H&Y stage between DLB and PDD patients showed no differences. Patients with DLB and PDD had more PD non-motor symptoms than did AD patients and controls and showed more severe sympathetic denervation than AD patients (Table 1).

Compared with the controls, dementia groups had more severe impairment in most of the cognitive domains. Most neuropsychological test results were similar among dementia groups, except for backward digit span. The activity of daily living scores were higher in the DLB and PDD groups compared to the AD group, suggesting a higher burden of motor impairment (Table 2).

With the exception of 1 control, all participants had subcortical whiter matter hyperintensities in the cholinergic pathways. The CHIPS scores were not correlated with increasing age in the dementia groups ($r = 0.168$, $p = 0.208$) and controls ($r = 0.071$, $p = 0.767$). CHIPS scores were unrelated to sex (male vs. female in control: 12.4 ± 9.4 vs. 10.7 ± 6.1; male vs. female in dementia groups: 35.9 ± 20.1 vs. 31.8 ± 13.4); with the presence of hypertension ([−] vs. [+] in control: 12.2 ± 8.5 vs. 10.5 ± 6.3; [−] vs. [+] in dementia: 30.4 ± 14.1 vs. 36.2 ± 16.8); with concurrent diabetes ([−] vs. [+] in control: 11.1 ± 8.1 vs. 13.3 ± 6.0; [−] vs. [+] in dementia: 32.2 ± 15.1 vs. 35.8 ± 17.9); and with smoking status (non-smoker vs. ex- and current smoker in control: 11.9 ± 8.0 vs. 7.5 ± 6.4; non-smoker vs. ex- and current smoker in dementia: 33.2 ± 15.6 vs. 29.3 ± 14.9)

The mean CHIPS scores were similar among the three dementia groups (AD vs. DLB vs. PDD = 34.6 ± 17.9 vs. 32.4 ± 14.1 vs. 31.8 ± 14.5, $p = 0.781$ by ANCOVA) and higher than those of controls (11.5 ± 7.6, $p = 0.001$ by ANCOVA). For the analysis of CHIPS in different brain regions, there were no significant differences among the AD, DLB, and PDD groups (Fig. 1). For the correlation analysis, CHIPS were correlated with MMSE, SOB scores of the CDR, and verbal and visuospatial memory domains in the dementia groups (Table 3).

4. Discussion

In this study of patients with parkinsonism and dementia, scores of cholinergic pathway hyperintensities were not different among AD, DLB, and PDD patients and were more elevated in the dementia groups than in controls. Memory domain dysfunction was associated with elevated WMH (CHIPS) score on MRI in patients with parkinsonism and dementia. Given the lack of differences in neuropsychological performance or subcortical hyperintensities in cholinergic tracts among the AD, DLB, and PDD groups, the results suggest that cognitive dysfunction in the spectrum of dementia and parkinsonism is related to cholinergic impairment and may reach the same level as those with vascular damage.

White matter hyperintensities are more prominent in AD than in healthy controls and are known as potential risk factors for conversion to dementia in MCI patients [14,15]. However, the association of WMHs in the PDD/DLB complex remains controversial in simple visual rating or volumetric analysis [15–18]. The recently developed WMH scale, CHIPS, has shown to better reflect cognitive dysfunction than simple WMH scales [19], and groups with higher CHIPS show more cognitive decline and less response to cholinesterase inhibitor treatment in