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Cortical thickness and hippocampal shape in pure vascular mild cognitive impairment and dementia of subcortical type

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Abstract

Background and purpose—The progression pattern of brain structural changes in patients with isolated cerebrovascular disease (CVD) remains unclear. To investigate the role of isolated CVD in cognitive impairment patients, patterns of cortical thinning and hippocampal atrophy in pure subcortical vascular mild cognitive impairment (svMCI) and pure subcortical vascular dementia (SVaD) patients were characterized.

Methods—Forty-five patients with svMCI and 46 patients with SVaD who were negative on Pittsburgh compound B (PiB) positron emission tomography imaging and 75 individuals with normal cognition (NC) were recruited.

Results—Compared with NC, patients with PiB(–) svMCI exhibited frontal, language and retrieval type memory dysfunctions, which in patients with PiB(–) SVaD were further impaired and accompanied by visuospatial and recognition memory dysfunctions. Compared with NC, patients with PiB(–) svMCI exhibited cortical thinning in the frontal, perisylvian, basal temporal and posterior cingulate regions. This atrophy was more prominent and extended further toward the lateral parietal and medial temporal regions in patients with PiB(–) SVaD. Compared with NC subjects, patients with PiB(–) svMCI exhibited hippocampal shape deformities in the lateral body, whilst patients with PiB(–) SVaD exhibited additional deformities within the lateral head and inferior body.

Conclusions—Our findings suggest that patients with CVD in the absence of Alzheimer's disease pathology can be demented, showing cognitive impairment in multiple domains, which is consistent with the topography of cortical thinning and hippocampal shape deformity.

Keywords

cortical thickness; hippocampal shape; Pittsburgh compound B PET; subcortical vascular dementia; subcortical vascular mild cognitive impairment

Introduction

Progressive patterns in cognitive decline and brain atrophy have been extensively investigated in patients with amnesic mild cognitive impairments (MCI) and dementia due to Alzheimer's disease (AD) [1,2]. However, few previous studies have investigated the nature of progression in subjects with cerebrovascular diseases (CVD) such as subcortical vascular MCI (svMCI) and subcortical vascular dementia (SVaD) [3,4]. It has been shown that frontal, language, visuospatial and memory functions are impaired in clinically diagnosed svMCI patients and that these dysfunctions are further impaired in cases of clinically diagnosed SVaD, consistent with the extent of cortical thinning [4]. However, language, visuospatial and memory dysfunctions, in addition to cortical thinning other than that of the frontal region, are commonly observed in patients with AD; as such, these features could be a result of patients having combined CVD and AD pathologies.

Memory dysfunction, known to be characteristic of AD, can also be identified in patients with ‘pure’ SVaD [5,6]. Previous studies suggest that memory dysfunction in pure SVaD patients might be due to disrupted prefrontal-subcortical circuits [7]. However, it remains possible that memory dysfunction in these patients could be related to the involvement of the hippocampus, due to its role in memory and vulnerability to ischaemia. A previous study has shown that hippocampal atrophy indeed occurs in pure SVaD [8]. However, whether hippocampal involvement is significant for pure svMCI and whether subregional involvement exhibits a specific pattern in pure svMCI and pure SVaD has not been elucidated.

In this study, patterns of cortical thinning and hippocampal atrophy in pure svMCI and pure SVaD patients, defined as those exhibiting a Pittsburgh compound B (PiB) retention ratio below 1.5 [9], were characterized to investigate the role of isolated CVD in cognitive impairment patients.

Methods

Participants

Sixty-seven patients with svMCI and 70 patients with SVaD, all of whom had been clinically diagnosed at Samsung Medical Center between September 2008 and August 2011, were prospectively recruited. Patients with SVaD met the diagnostic criteria for vascular dementia as determined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition. All SVaD patients exhibited significant ischaemia as determined by MRI scans, defined as a cap or band ≥ 10 mm as well as a deep white matter lesion ≥ 25 mm (a modification of the Fazekas ischaemia criteria) [10]. The 45 SVaD patients have been described previously regarding clinical characteristics and [^{11}C]PiB positron emission tomography (PET) findings [9]. Patients with svMCI were diagnosed using the Petersen criteria [11] with the inclusion of the following modifications: (i) subjective cognitive complaints by the patient or his/her caregiver; (ii) normal activity of daily living; (iii) objective cognitive decline assessment below the 16th percentile on neuropsychological tests; (iv) absence of dementia; and (v) presence of a subcortical vascular feature defined as both a focal neurological symptom/sign and significant ischaemia on MRI, as for SVaD. Patients with territory infarctions and those with high signal abnormalities on the MRI due to radiation injury, multiple sclerosis, vasculitis or leukodystrophy were excluded.

In all, 32.8% (22/67) of the patients diagnosed with svMCI and 32.9% (23/70) of the patients diagnosed with SVaD were excluded due to PiB PET scan results that were positive. One patient with PiB(–) SVaD was excluded due to a neuropsychological test not being completed. As a result, a total of 45 PiB(–) svMCI and 46 PiB(–) SVaD patients were included. The patients recruited frequently exhibited gait disturbance which was noted as a focal neurological sign [66.7% of PiB(–) svMCI patients and 87% of PiB(–) SVaD patients]. The MRI findings for each patient are shown in Fig. S1. Due to poor MRI quality, one patient with PiB(–) svMCI was excluded from analysis of cortical thickness and three patients with PiB(–) svMCI were excluded from analysis of hippocampal shape.

Seventy-five normal cognition (NC) subjects from the neurology clinic at Samsung Medical Center who had no history of neurological or psychiatric illnesses and no abnormalities detected during neurological examination were also recruited. They were determined to be cognitively normal after undergoing the same neuropsychological testing and MRI scanning.

The study was approved by the Institutional Review Board of the Samsung Medical Center. Written informed consent was obtained from all the participants.

Neuropsychological tests

All participants underwent neuropsychological tests using a standardized neuropsychological battery [12]. The battery contains digit span (forward and backward), the Boston Naming Test (BNT), Rey–Osterrieth Complex Figure Test (RCFT; copying, immediate and 20-min delayed recall, and recognition), Seoul Verbal Learning Test (SVLT; three learning-free recall tests of 12 words, 20-min delayed recall test for those 12 items, and a recognition test), a phonemic and semantic Controlled Oral Word Association Test (COWAT) and the Stroop test (word and color reading of 112 items during a 2-min period).

[¹¹C]PiB PET imaging

All patients completed a [¹¹C]PiB PET scan at Samsung Medical Center or Asan Medical Center. All subjects completed the same type of PET scan with a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI, USA). The detailed radiochemistry profiles, scanning protocol and PiB PET data analysis are described in Data S1 and a previous study [9].

Acquisition of three-dimensional MR images

Using the same 3.0-T MRI scanner (Philips 3.0T 164 Achieva, Eindhoven, the Netherlands), 3D T1 turbo field echo MR images were acquired from all participants as previously described [13]. Detailed MRI parameters are described in Data S2.

Measurement of white matter hyperintensity volume and lacunes

White matter hyperintensity (WMH) volume (in milliliters) was quantified on fluid-attenuated inversion recovery (FLAIR) images using an automated method [14]. Lacunes were manually counted. Detailed methods are described in Data S3.

Image processing for cortical thickness measurements

Images were processed using the standard Montreal Neurological Institute anatomical pipeline. The detailed image processing methods are described in Data S4 and a previous study [13].

Image processing for hippocampal shape deformity

Our shape analysis method is derived from boundary surfaces of the hippocampus; the detailed image processing methods are described in Data S5.

Statistical analysis

For descriptive statistics, the chi-squared test and analysis of variance followed by Bonferroni's *post hoc* analysis were used to compare the NC, PiB(–) svMCI and PiB(–) SVaD groups. To evaluate the differences in neuropsychological test scores between the three groups, analysis of covariance (ANCOVA) was performed after adjusting for age, gender and education level followed by *post hoc* analysis using Bonferroni's method. Bonferroni's correction was also used to correct for the multiple testing. Mean cortical thickness and hippocampal volumes were compared between the three groups using ANCOVA after controlling for age, gender, education level and intracranial volume (ICV), followed by *post hoc* analysis using Bonferroni's method. Statistical analyses were performed with PASW Statistics 18.0 (Predictive Analysis Software, Chicago, IL, USA).

The localized differences in hippocampal shape and cortical thickness between the NC, PiB(–) svMCI and PiB(–) SVaD groups were analyzed using a general linear model on a vertex-by-vertex basis. As for hippocampal shape and cortical thickness analysis, age, gender, education level and ICV were controlled. The hippocampal surface model had 5124 vertices and the cortical surface model contained 81 924 vertices; thus correction for multiple comparisons was performed by random field theory at a corrected probability value of 0.05 [15]. Group-wise differences in voxel-wise hippocampal shape and regional cortical thickness were compared using Matlab 7.11 for Windows (Math Works, Natick, MA, USA).

In order to certify the correlation between neuropsychological test scores (which had significant differences between groups) and structural MRI features in the regions where the differences occur between groups [NC versus PiB(–) svMCI, NC versus PiB(–) SVaD or PiB(–) svMCI versus PiB(–) SVaD], multiple linear regression analysis for neuropsychological results was performed after controlling for age, gender, education and ICV. The mean cortical thicknesses of the areas where there were significant differences between groups were used as predictors when evaluating relationships with language, visuospatial or frontal executive functions. The mean hippocampal deformities of the areas where there were significant differences between groups were used as predictors when evaluating relationships with memory function.

Results

Baseline characteristics

There were no differences in the prevalence of the *APOE ε4* carrier or cardiovascular risk factors between PiB(–) svMCI and PiB(–) SVaD patients. However, PiB(–) SVaD patients exhibited larger WMH volume and more lacunes than PiB(–) svMCI patients (Table 1).

Neuropsychological results

Compared with NC subjects, PiB(–) svMCI patients exhibited poorer performance in language (BNT), memory (immediate/delayed recall on both RCFT and SVLT) and frontal/executive functions (COWAT animal/supermarket/phonemic and Stroop color reading). Compared with NC subjects, PiB(–) SVaD patients exhibited poorer performance in all

cognitive tests except digit span forward. In comparison to patients with PiB(–) svMCI, PiB(–) SVaD patients exhibited further declines in multiple cognitive domains, including language (BNT), visuospatial (RCFT copy), memory (immediate/delayed recall/recognition on both RCFT and SVLT) and frontal/executive function (COWAT animal/supermarket/phonemic and Stroop color reading) (Table 2).

Topography of cortical thinning

Comparisons of mean cortical thicknesses between NC subjects and patients with PiB(–) svMCI or PiB(–) SVaD are shown in Fig. 1a. The topography of cortical thinning is shown in Fig. 2. Compared with NC subjects, PiB(–) svMCI patients exhibited significant cortical thinning in bilateral inferior prefrontal, superior medial frontal, inferior parietal and lateral temporal regions, as well as the posterior cingulate and lingual gyrus (Fig. 2a). Compared with NC subjects, PiB(–) SVaD patients exhibited statistically significant thinning in the left inferior parietal, prefrontal, right medial superior frontal and lingual regions (Fig. 2b). A comparison between PiB(–) svMCI and PiB(–) SVaD patients revealed that those with PiB(–) SVaD showed cortical thinning in prefrontal, superior medial frontal, orbitofrontal and inferior parietal areas (Fig. 2c).

Hippocampal volume and shape analyses

Comparisons of total volume of hippocampus between NC subjects and patients with PiB(–) svMCI or PiB(–) SVaD are shown in Fig. 1b. Hippocampal shape analyses between the groups are shown in Fig. 3. PiB(–) svMCI patients exhibited inward deformity in the bilateral lateral body compared with NC subjects (Fig. 3a). PiB(–) SVaD patients exhibited inward deformity in the bilateral lateral head and inferior body compared with NC subjects (Fig. 3b). Finally, PiB(–) SVaD patients exhibited inward deformity in the bilateral lateral head compared with PiB(–) svMCI patients (Fig. 3c).

Correlation between neuropsychological results and structural MRI features

There were significant correlations between the neuropsychological test scores (which had significant differences between groups) and structural MRI features in the regions where there were significant differences between groups [NC versus PiB(–) svMCI, NC versus PiB(–) SVaD or PiB(–) svMCI versus PiB(–) SVaD] (Table S1): (i) in NC and PiB(–) svMCI groups, the mean cortical thickness correlated with scores in language and frontal/executive functions, and the mean hippocampal deformity correlated with scores in memory tests (immediate recall/delayed recall) on both RCFT and SVLT; (ii) in NC and PiB(–) SVaD or in PiB(–) svMCI and PiB(–) SVaD, the mean cortical thickness correlated with scores in all cognitive tests in language, visuospatial and frontal/executive functions, and the mean hippocampal deformity correlated with scores in all memory tests.

Discussion

Our major findings are as follows. First, patients with pure svMCI presented with frontal, language and retrieval type memory dysfunctions; these functions were further impaired and accompanied by visuospatial and recognition memory dysfunctions in patients with pure SVaD. Secondly, patients with pure svMCI exhibited cortical atrophy in frontal, perisylvian,

basal temporal and posterior cingulate regions; atrophy in these regions was more prominent and extended further toward the lateral parietal and medial temporal regions in patients with pure SVaD. Thirdly, hippocampal atrophy progressed in a specific pattern in that patients with pure svMCI exhibited focal atrophy in the lateral body, whilst patients with pure SVaD exhibited additional atrophy in the lateral head and inferior body. Taken together, our findings suggest that patients with CVD in the absence of AD pathology could be demented, showing cognitive impairment in multiple domains, which is consistent with the topography of cortical thinning and hippocampal shape deformity.

Our first major finding was that patients with pure svMCI exhibited frontal, language and retrieval type memory dysfunctions, which, in patients with pure SVaD, were further impaired together with visuospatial and recognition memory dysfunctions. The relevance of CVD as a causative factor for cognitive impairment, especially other than frontal dysfunction, remains unclear. Although some recent researches have raised that possibility, those particular studies did not exclude patients with coexisting AD pathology [16,17]. Considering that patients with amyloid burden were excluded in the current study, our findings suggest that patients with isolated CVD exhibit multidomain cognitive dysfunction, which is not limited to frontal dysfunction even in the MCI stage. Our findings also suggest that patients with CVD in the absence of AD pathology could be demented, showing cognitive impairment in multiple domains, including visuospatial and recognition memory dysfunctions.

Our second major finding was that pure svMCI patients exhibited cortical atrophy in frontal, perisylvian, basal temporal and posterior cingulate regions. Previous studies have shown that CVD is associated with brain atrophy [18,19]. Moreover cortical atrophy in pure SVaD patients has been previously reported [13]. However, this is the first study to show that cortical atrophy can exist even in pure svMCI patients. There was also a specific pattern of cortical thinning in patients with pure svMCI and pure SVaD, which was consistent with neuropsychological findings. In patients with pure svMCI, frontal thinning could account for frontal dysfunction, whilst cortical thinning in the basal temporal area could account for language dysfunction and cortical thinning in posterior cingulate regions could also account for memory dysfunction. The regions where pure svMCI patients exhibited cortical thinning were further exacerbated in pure SVaD patients. In addition, cortical thinning in pure SVaD patients was extended to the lateral parietal and medial temporal regions, which might be the cause of the further impairment in visuospatial and recognition memory functions, respectively.

It was observed that the type of memory dysfunction in pure svMCI was retrieval defect, which seems to be related to disruption of the frontal-subcortical circuit [7]. However, our finding that pure svMCI patients exhibited hippocampal atrophy suggests that isolated CVD may affect retrieval-type memory impairments through involvement of the hippocampus, as well as frontal-subcortical disruption. Indeed, a recent study of functional MRI suggested that retrieval of memories requires activity of the hippocampus [20].

Our final major finding was that there appear to be specific patterns in deformities of hippocampal shape in patients with pure svMCI and pure SVaD. That is, pure svMCI

patients exhibited hippocampal atrophy in the lateral body [cornu ammonis (CA) 1], whilst the relevant hippocampal areas in pure SVaD patients extended to the lateral head (CA1) and inferior body (subiculum). Previous studies have shown that the CA1 subregions (head and body of hippocampus) are susceptible to ischaemia [21]. These regions are also known to be vulnerable to AD pathologies [22]. However, patients with AD pathologies revealed a different order of involvement of the hippocampal subregions from those with CVD. Specifically, patients with amnesic MCI exhibited hippocampal shape changes mainly in the head portion [23], whilst AD patients exhibited hippocampal deformity in the head and lateral body [23]. There are several possible interpretations with regard to the hippocampal atrophy in the pure SVaD patients. First, it is possible that CVD might have disrupted the connection between the hippocampus and the cortical areas, leading to secondary degeneration and eventually resulting in hippocampal atrophy. Secondly, chronic ischaemia may have directly insulted the hippocampus which is one of the most vulnerable structures to ischaemia [24,25]. Indeed, chronic impaired blood flow may have directly damaged the hippocampus, especially in the CA1 subregion [21].

The strengths of our study were its prospective setting, standardized PiB PET/MRI imaging protocols, standardized phenotyping of cognitive impairment and a large sample size. However, this study has several limitations. First, PiB PET was not performed in the NC group. Previous studies have shown that approximately 20% of NC subjects are PiB(+) and that amyloid deposition is associated with cortical thinning prior to development of cognitive impairment [26]. Thus, our data may have underestimated the cognitive impairment and structural changes in PiB(–) svMCI and PiB(–) SVaD groups. Secondly, differences between pure svMCI and pure SVaD patients could only be inferred due to the cross-sectional nature of our study. Future studies with PiB(–) NC or longitudinal follow-up PiB(–) svMCI will be needed to solve these limitations. Thirdly, PiB PET may not be sufficiently sensitive to detect soluble amyloid oligomers, diffuse amyloid plaques or neurofibrillary-tangle-predominant AD. In addition, although patients with dementia with Lewy bodies or tau frontotemporal dementia were excluded using clinical criteria, patients with synuclein or tau pathologies might have been included in the present study. Fourthly, additional tests for evaluation of executive function such as the Trail Making Test and London Tower Test may provide important information in patients with svMCI or SVaD.

Taken together, our results suggest that the progression of cognitive dysfunction in multiple domains and associated structural changes occur with a specific pattern as patients with isolated CVD progress from MCI to dementia. Although longitudinal studies are still needed, the evidence suggests that, as CVD progresses, frontal, language and memory dysfunction appears in the early stage of cognitive impairment (pure svMCI), which further declines along with attention, visuospatial and recognition memory dysfunction in the later stages of cognitive impairment (pure SVaD). The corresponding structural changes can be seen in cortical thickness and hippocampal shape.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Comparison of overall mean cortical thickness (a) and hippocampal volume (b) between NC, PiB(-) svMCI and PiB(-) SVaD groups. Error bars represent 95% confidence intervals of mean cortical thickness. NC, normal cognition; PiB, Pittsburgh compound B; svMCI, subcortical vascular mild cognitive impairment; SVaD, subcortical vascular dementia.

Figure 2.
(a)–(c) Statistical representation of cortical thickness in NC, PiB(-) svMCI and PiB(-) SVaD groups.

Figure 3.

(a)–(c) Hippocampal shape analysis in NC, PiB(-) svMCI and PiB(-) SVaD groups.

Table 1

Subject characteristics

	NC (N = 75)	PiB(−) svMCI (N = 45)	PiB(−) SVaD (N = 46)
Demographics			
Age	63.6 ± 8.2	72.1 ± 6.6 *	71.9 ± 7.3 *
Male:female	18:57	16:29	22:24 *
Education	12.0 ± 4.8	8.9 ± 5.3 *	8.3 ± 4.8 *
Cardiovascular risk factors, n (%)			
Hypertension	14 (18.7)	38 (84.4) *	36 (78.3) *
Diabetes	31 (41.3)	12 (26.7)	12 (26.5)
Hyperlipidemia	18 (24.0)	14 (31.1)	20 (43.5) *
MRI markers of cerebrovascular disease			
WMH volume (ml)	1.3 ± 1.7	31.7 ± 16.0 *	37.5 ± 13.3 *, †
Lacune, n	0.5 ± 1.1	8.4 ± 8.6 *	20.0 ± 17.8 *, †
MMSE score	28.8 ± 1.5	26.6 ± 2.4 *	21.7 ± 4.5 *, †
ICV (ml)	1345.3 ± 114.3	1353.7 ± 102.7	137.6 ± 116.9

NC, normal cognition; PiB, Pittsburgh compound B; svMCI, subcortical vascular mild cognitive impairment; SVaD, subcortical vascular dementia; WMH, white matter hyperintensities; MMSE, Mini-Mental State Examination; ICV, intracranial volume.

* $P < 0.05$ between NC and PiB(−) svMCI or between NC and PiB(−) SVaD groups;

† $P < 0.05$ between PiB(−) svMCI and PiB(−) SVaD groups.

Table 2

Comparison of neuropsychological performance outcomes

	NC (N = 75)	PiB(-) svMCI (N = 45)	PiB(-) SVaD (N = 46)
Attention			
Digit span forward	6.4 ± 1.4	5.1 ± 1.3	4.8 ± 1.3
Digit span backward	4.4 ± 1.4	3.2 ± 1.1	2.4 ± 1.3 *
Language			
K-BNT	50.6 ± 5.7	41.2 ± 9.2 *	31.6 ± 10.9 *,†
Visuospatial functions			
RCFT copy score	33.5 ± 2.1	28.1 ± 7.0	19.5 ± 10.5 *,†
Memory			
RCFT immediate recall	18.2 ± 5.0	11.2 ± 6.0 *	4.9 ± 4.9 *,†
RCFT delayed recall	17.5 ± 4.8	11.1 ± 5.3 *	4.0 ± 4.4 *,†
RCFT recognition	20.2 ± 1.5	19.6 ± 1.9	16.3 ± 3.5 *,†
SVLT immediate recall	22.5 ± 4.4	16.9 ± 5.4 *	12.0 ± 4.6 *,†
SVLT delayed recall	7.6 ± 2.1	4.8 ± 2.8 *	1.7 ± 2.0 *,†
SVLT recognition	21.6 ± 1.7	19.9 ± 2.1	17.3 ± 2.8 *,†
Frontal/executive functions			
COWAT animal	17.3 ± 4.9	12.2 ± 3.5 *	7.8 ± 3.3 *,†
COWAT supermarket	18.6 ± 5.6	13.3 ± 5.2 *	6.1 ± 4.5 *,†
COWAT phonemic	28.7 ± 11.6	15.9 ± 9.1 *	7.2 ± 5.7 *,†
Stroop color reading	93.5 ± 18.3	64.3 ± 24.7 *	26.2 ± 26.8 *,†

NC, normal cognition; K-BNT, Korean version of the Boston Naming Test; RCFT, Rey–Osterrieth Complex Figure Test; SVLT, Seoul Verbal Learning Test; COWAT, Controlled Oral Word Association Test.

* $P < 0.05$ between NC and PiB(-) svMCI or NC and PiB(-) SVaD groups;

† $P < 0.05$ between PiB(-) svMCI and PiB(-) SVaD groups; ANCOVA was performed after adjusting for age, gender and education level followed by *post hoc* analysis using the Bonferroni method. Bonferroni's correction was also used to correct for multiple testing of neuropsychological results.