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Hippocampal and cortical atrophy in amyloid-negative mild cognitive impairments: comparison with amyloid-positive mild cognitive impairment

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ABSTRACT

Although patients with amnestic mild cognitive impairment (aMCI) are at higher risk of developing Alzheimer's disease (AD), their pathologies could be heterogeneous. We aimed to evaluate structural changes in amyloid-negative and amyloid-positive aMCI patients. Forty-eight aMCI patients who underwent Pittsburgh compound B (PiB) positron emission tomography were recruited. They were classified as PiB (−) aMCI (N = 16) and PiB (+) (N = 32). Hippocampal shape and regional cortical thickness were compared with 41 subjects with normal cognition (NC). Relative to NC, PiB(−) aMCI exhibited hippocampal deformity in the right cornu ammonis 1, whereas PiB(+) aMCI exhibited hippocampal deformity in bilateral subiculum and cornu ammonis 1 subregions. Relative to NC, PiB(−) aMCI showed cortical thinning in the left medial prefrontal and right anterior temporal regions, whereas PiB(+) aMCI exhibited cortical thinning in bilateral medial temporal regions, temporoparietal junctions and precuneus, and prefrontal cortices. Our findings suggest that structural changes in PiB(−) aMCI might be due to several possible pathologic changes, whereas structural changes in PiB(+) aMCI reflect AD-like structural changes.

1. Introduction

Although amnestic mild cognitive impairment (aMCI) refers to a prodromal stage of Alzheimer's disease (AD) (Morris et al., 2001), recent research findings have suggested that aMCI patients might be pathologically heterogeneous. Studies have revealed that aMCI patients exhibit varying degrees of AD pathologies from Braak stage I to V (Bennett et al., 2005; Petersen et al., 2006). An estimated 20%–50% of aMCI patients are pathologically normal or exhibit other pathologies such as vascular disease, Lewy bodies, tauopathies, and hippocampal sclerosis (Bennett et al., 2005; Morris et al., 2001; Schneider et al., 2009).

Premortem detection of amyloid burden is now possible through positron emission tomography (PET) imaging using ^{11}C-Pittsburgh compound B (PiB) (Klunk et al., 2004). The frequency of PiB-positivity is reported to be 52%–87% in aMCI patients (Pike et al., 2007; Rowe et al., 2007; Wolk et al., 2009). However, few studies have evaluated structural changes in patients with PiB-positive (PiB(+)) and PiB-negative (PiB(−)) aMCI (Wolk et al., 2009). Patients with PiB(+) aMCI might be closer to AD in terms of structural changes because aMCI patients without amyloid burden could be excluded. As for PiB(−) aMCI, there are several possibilities. First, structural changes in PiB(−) aMCI patients could be absent because intrapersonal variability of neuropsychological test scores might influence a PiB(−) aMCI diagnosis. Alternatively,

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PiB(−) aMCI might represent a heterogeneic outcome of several possible causes that affect structural changes in the brain.

In this study, we analyzed the distribution of hippocampal shape deformities and cortical thinning in PiB(+) and PiB(−) aMCI patients.

2. Methods

2.1. Participants

We prospectively recruited 48 patients who met the criteria for aMCI (Seo et al., 2007) and underwent ^{11}C-PiB PET scanning at Samsung Medical Center (Seoul, Republic of Korea) between February 2009 and July 2011. The criteria were based on guidelines proposed by Petersen et al. (1999) and included the following: (1) subjective memory complaint by subjects or caregivers; (2) normal general cognitive function as defined by scores on the Mini-Mental State Examination (MMSE) greater than or equal to −1.0 SD of the norms for age- and education-matched normal subjects; (3) normal activities of daily living (ADL), as judged both clinically and on the ADL scale described subsequently; (4) objective memory decline below −1.0 SD on either verbal or visual memory tests (this cutoff value has been used in previous studies; Supplementary Method 1); and (5) not demented. Patients with aMCI who had severe periventricular or deep white matter ischemia, as indicated by a score of ≥3 on the Fazekas ischemic scale, were excluded. We also excluded patients with clinical presentation reminiscent of other dementias such as dementia with Lewy bodies (DLB) or frontotemporal lobar degeneration (FTLD). ADL was assessed by a questionnaire form, the Seoul Instrumental ADL, which was described in a previous study (Seo et al., 2007).

We recruited 41 age-, gender-, and education-matched individuals with normal cognition (NC) who had no previous history of neurologic or psychiatric illnesses. The NC subjects showed normal cognitive function on the MMSE and all neuropsychological tests (described in the next section). This study was approved by the Institutional Review Board of Samsung Medical Center, and informed consent for participation was obtained from every participant.

All participants underwent comprehensive interviews and neurologic examinations, as described in previous studies (Seo et al., 2007). Participants with current or past neurologic or psychiatric illnesses, such as schizophrenia, major depressive disorders, epilepsy, brain tumors, encephalitis, and severe head trauma, were excluded. In addition, patients with severe hearing or visual loss, aphasia, severe cardiac disorders, severe respiratory illnesses, malignancies, and hepatic or renal disorders were excluded. Blood tests for all participants included a complete blood count, blood chemistry tests, vitamin B12/folate, syphilis serology, and thyroid function tests. On magnetic resonance imaging (MRI), patients with structural lesions, such as tumors, traumatic brain injuries, or hydrocephalus were excluded.

2.2. Neuropsychological assessments

All participants underwent a standardized neuropsychological battery called the Seoul Neuropsychological Screening Battery, which contains tests for attention, language, praxis, 4 elements of Gerstmann syndrome, visuoconstructive function, verbal and visual memory, and frontal/executive function (Seo et al., 2007). Among these, scorable tests were as follows: digit span (forward and backward), the Korean version of the Boston Naming Test (K-BNT), the Rey-Osterrieth Complex Figure Test (RCFT; copying, immediate and 20-minute delayed recall, and recognition), Seoul Verbal Learning Test (SVLT; immediate, 20-minute delayed recall, and recognition), phonemic and semantic Controlled Oral Word Association Test (COWAT), and the Stroop Test (word and color reading). Cognitive function was categorized into memory, language, visuospatial, and frontal executive function and considered abnormal when scores in the relevant neuropsychological tests were below −1.0 SD of the norm as detailed in a previous study (Seo et al., 2007).

2.3. PiB-PET acquisition

[11C] PiB-PET scanning was performed using an identical scanner (GE Medical Systems, Milwaukee, WI, USA) and image parameters. The detailed scanning protocol was described in a previous study (Lee et al., 2011).

2.4. PiB-PET data analysis

To measure PiB retention, we used standardized uptake value (SUV) ratios, referring to the cerebral cortical region to cerebellum retention ratio. The cerebellum was used as a reference region as described in a previous study (Lee et al., 2011). The cerebral cortical volume of interest (VOIs) chosen for this study consisted of bilateral frontal (superior and middle frontal gyri; medial part of superior frontal gyrus; opercular part of inferior frontal gyrus; triangular part of inferior frontal gyrus; supplementary motor area; orbital part of superior, middle, and inferior orbital frontal gyri; rectus and olfactory cortex), posterior cingulate gyri, parietal (superior and inferior parietal, supramarginal and angular gyri, and precuneus), lateral temporal (superior, middle, and inferior temporal gyri and Heschl gyri), and occipital (superior, middle, and inferior occipital gyri, cuneus, calcarine fissure, and lingual and fusiform gyri) VOIs. Regional cerebral cortical SUVRs were calculated by dividing each cortical VOI's SUV by the mean SUV of the cerebellar cortex (cerebellum crus1 and crus2). Global PiB retention ratios were calculated from the volume-weighted average SUV ratio of bilateral 28 cerebral cortical VOIs. Patients were considered PiB-positive if their global PiB retention ratio was >1.5 (Lee et al., 2011). We also calculated 4 lobar (frontal, parietal, temporal, and posterior cingulate) PiB retention ratios.

2.5. MRI acquisition

MRIs were performed using a 3.0-Tesla MRI scanner (Philips 3.0T Achieva) at Samsung Medical Center. Three-dimensional (3D) T1 Turbo Field Echo and 3D fluid-attenuated inversion recovery (FLAIR) was acquired in all 89 subjects (48 aMCI patients and 41 controls). The 3D T1 Turbo Field Echo MR images were acquired using the following imaging parameters: sagittal slice thickness = 1.0 mm, overcontiguous slices with 50% overlap; no gap; repetition time = 9.9 msec; echo time = 4.6 msec; flip angle 8°; matrix size 240 × 240 pixels, reconstructed to 480 × 480 over a field of view (FOV) of 240 mm. The following parameters were used for 3D FLAIR images: axial slice thickness = 2 mm, no gap, repetition time = 11,000 msec, echo time = 125 msec, flip angle of 90°, and matrix size of 512 × 512 pixels.

2.6. Measurement of white matter hyperintensity volume

Using FLAIR images, white matter hyperintensity (WMH) volumes were automatically measured in aMCI patients. The measuring procedures have been previously described (Jeon et al., 2011).