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Research article

Differential patterns of regional cerebral hypometabolism according to the level of cerebral amyloid deposition in patients with amnestic mild cognitive impairment

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HIGHLIGHTS

- Different rCMglu pattern in aMCI according to cerebral amyloid deposition is shown.
- AMCI group has different neurodegeneration patterns according to amyloid level.
- Amyloid negative aMCI group might include non-AD neurodegenerative condition.

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ABSTRACT

Although amnestic mild cognitive impairment (aMCI) with high cerebral deposition of amyloid-beta proteins (Aβ) could be classified as a prodromal state of Alzheimer's disease (AD) dementia, aMCI with the absence of or very little cerebral Aβ deposition is likely related to other pathophysiological processes. Thus, the present study aimed to investigate the differential patterns of regional cerebral glucose metabolism (rCMglu) according to the level of Aβ burden in the brains of patients with aMCI. This study included 25 patients with aMCI and 33 cognitively normal (CN) elderly individuals who underwent a comprehensive clinical examination, ^{11}C-labelled Pittsburgh Compound B (PiB) positron emission tomography (PET) scans, and ^{18}F-fluorodeoxyglucose (FDG) PET scans. Based on cerebral PiB retention, the aMCI subjects were divided into low Aβ (aMCI−, n = 10) and high Aβ (aMCI+, n = 15) subgroups, and differences in rCMglu among the CN group and aMCI subgroups were estimated on a voxel-by-voxel basis. Compared with the CN group, rCMglu was decreased in the bilateral medial temporal regions of the aMCI− subgroup and in the medial temporal cortices as well as the right precuneus of the aMCI+ subgroup. Additionally, rCMglu was lower in the right precuneus of the aMCI+ subgroup compared with the aMCI− subgroup. The present findings indicate that, even though both aMCI subgroups were phenomenologically very similar, the patients with aMCI− exhibited a markedly different regional pattern of functional neurodegeneration compared with the aMCI+ patients.

1. Introduction

Although amnestic mild cognitive impairment (aMCI) is regarded as the prodromal stage of Alzheimer's disease (AD) dementia [1], recent studies have suggested that aMCI may be pathologically and etiologically heterogeneous. Studies using ^{11}C-labelled Pittsburgh compound B (PiB) positron emission tomography (PET) demonstrated that many aMCI patients do not exhibit a sufficient deposition of cerebral amyloid-beta proteins (Aβ) to warrant a diagnosis of AD [2,3]. Although aMCI with high cerebral deposition of Aβ (aMCI+) could be classified as the prodromal state of AD dementia [1,4], aMCI with the absence of or very little cerebral Aβ deposition (aMCI−) is likely related to other pathophysiological conditions.

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The use of ^{18}F-fluorodeoxyglucose-PET (FDG-PET) to measure regional cerebral glucose metabolism (rCMglu) is a reliable index of regional neuronal or synaptic activity [5,6]. Therefore, FDG-PET could be very useful for the identification of specific functional neuronal injuries and/or neurodegenerative patterns related to AD or other neurodegenerative processes [7]. Several previous studies have reported that aMCI patients who converted to AD dementia had different rCMglu patterns compared to those who did not [8,9]. However, few studies have compared the region-specific hypometabolism patterns of aMCI subgroups classified by level of amyloid burden. Thus, the present study aimed to investigate the functional neurodegeneration patterns of patients with aMCI− and aMCI+ using rCMglu as measured by FDG-PET; the rCMglu pattern results were compared between the aMCI subgroups and with a cognitively normal (CN) group of elderly individuals.

2. Methods

2.1. Participants

The present study included 25 patients with aMCI and 33 CN elderly individuals. All patients with aMCI were recruited from among those who visited the Dementia and Age-Associated Cognitive Decline Clinic at Seoul National University Hospital and met the Petersen criteria [10]. The detailed inclusion and exclusion criteria have been described previously by our research group [11].

Informed consent was obtained from all subjects and their relatives prior to the study, and the institutional review board of Seoul National University Hospital, Seoul, South Korea approved the study protocol.

2.2. Clinical assessments

All subjects were examined at baseline according to the protocols of the Korean version of Consortium to Establish a Registry for AD (CERAD) Assessment Packet [12,13] and received eight tests in the CERAD neuropsychological battery by psychiatrists and neuropsychologist with advanced training in dementia research. Severity of depressive symptoms was assessed using the Hamilton Rating scale for Depression (HRSD). Subsequently, all subjects underwent multi-modal brain imaging that included PiB-PET, FDG-PET, and magnetic resonance imaging (MRI) scans. The total and memory scores on the CERAD neuropsychological battery (CERAD-TS and CERAD-MS, respectively) were calculated. The CERAD-TS is the sum of the scores from the seven tests in the battery [14], while the CERAD-MS is the sum of the scores from the four episodic memory tests in the battery [11]. Additionally, the presence or absence of stroke, diabetes, hyperlipidemia, history of transient ischemic attacks, hypertension, and/or coronary artery disease were systematically assessed to create a composite score for vascular risk score (VRS); the VRS is the sum of the factors (if present) and ranges from 0 to 6 [15]. A panel consisting of three psychiatrists with expertise in dementia research made all clinical decisions, including the Clinical Dementia Rating (CDR), after a review of all available raw data.

2.3. PET image acquisition and preprocessing

All ^{11}C-PiB PET scans were performed using the ECAT EXACT47 scanner (Siemens-CTI; Knoxville, TN, USA), which has an intrinsic resolution of 5.2 mm full width at half maximum (FWHM); the ^{11}C-PiB PET image acquisition process and preprocessing details have been described previously in a study from our research group [11]. The images were classified as PiB-positive if the mean ^{11}C-PiB retention value was >1.4 in one of the following regions of interest: frontal, lateral temporal, lateral parietal, posterior cingulate-precuneus, and/or basal ganglia (BG) [16].

Each subject also underwent FDG-PET using the above mentioned PET scanner; the present study analyzed the images of 47 contiguous transverse planes with a 3.4 mm thickness for a longitudinal field of view of 16.2 cm. All FDG-PET scans were performed in a dimly lit room with minimal auditory stimulation during both the injection and PET scanning. Subjects took a supine position with their eyes closed during the scanning to minimize the confounding effects of any visual activity. The imaging data were preprocessed using Statistical Parametric Mapping 12 (SPM12; Institute of Neurology, University College of London, UK) implemented in Matlab 2014b (Mathworks, Inc.; Natick, MA, USA). First, the FDG-PET images were coregistered to individual T1 MRI images. Next, the transformation parameters obtained from the spatial normalization of the individual T1 MRI images to the Montreal Neurological Institute (MNI) template were applied to the spatial normalization of the T1-coregistered FDG-PET images to the standard MNI space. Images smoothed by convolution using an isotropic Gaussian Kernel with 12 mm FWHM were used for voxel-wise analyses. The interval between conducting the PiB-PET and FDG-PET scans and the clinical assessments was less than 3 months for each subject.

2.4. Statistical analysis

The demographic and clinical data of the CN, aMCI+, and aMCI− groups were compared using one-way analysis of variance (ANOVA) in conjunction with Bonferroni correction for continuous variables and the Chi-squared test for proportions and categorical data. All statistical analyses not performed using SPM12 were conducted using SPSS software (version 22.0, SPSS Inc.; Chicago, IL, USA), and two-tailed p values < 0.05 were considered to indicate statistical significance.

Differences in rCMglu among the groups were estimated on a voxel-by-voxel basis using analysis of covariance (ANCOVA) in SPM12 with age and sex as covariates. The resulting set of t values constituted the SPM (T) map, which was then transformed into a normal distribution to provide a SPM (Z) map. The voxel-wise results of the comparisons between the CN group and each aMCI subgroup are displayed at a p value < 0.001 (uncorrected), with an extent threshold of >100 contiguous voxels. Given the relatively small sample size, the significance threshold was set at $p < 0.001$ to prevent overlooking novel findings due to an excessively conservative threshold. Furthermore, to compare differential rCMglu patterns between the aMCI+ and aMCI− subgroups, a relatively liberal statistical threshold of $p < 0.01$ (uncorrected), with an extent threshold of >100 contiguous voxels, was applied due to the exploratory nature of this particular analysis. The MNI coordinates of the local maximum of each voxel cluster were automatically calculated in SPM12 and transformed into Talairach and Tournoux coordinates [17] using the min2tal program (http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/).

3. Results

The demographic and clinical characteristics of the subjects are summarized in Table 1. There were no significant differences in age, education, sex, VRS, HRSD or proportion of apolipoprotein E ε4 carriers among the CN, aMCI−, and aMCI+ groups. The CDR sum of boxes score of the aMCI+ and aMCI− subgroups did not differ significantly from each other, but both aMCI subgroups had significantly lower scores on most neuropsychological tests compared with the CN group. Additionally, the aMCI+ subgroup had a lower score on the word list memory (WLM) test of the CERAD compared