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Detection of Prodromal Alzheimer's Disease in Patients with Depression and Mild Cognitive Impairment Using ^{11}C-PIB PET: Preliminary Study

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Background: There is increasing evidence of an empirical link between late-life depression and cognitive impairment. Depressive symptoms may be the earliest identifiable clinical stage of dementia. In contrast, depression may represent an independent risk factor predisposing to dementia disorders, including Alzheimer's disease (AD). Among individuals with amnestic mild cognitive impairment and depression (aMCID), it is largely unknown who has brain amyloid deposition and will progress to AD. We employed the amyloid PET imaging using ^{11}C-Pittsburgh Compound B (^{11}C-PiB) to determine the presence of AD pathology in patients with aMCID. We examined differences in the clinical or radiological features between subjects with aMCID with amyloid deposition and those without. **Methods:** Twelve patients with aMCID (10 multiple-domain aMCID, 2 single-domain aMCID) underwent ^{11}C-PiB PET, brain MRI, and neuropsychological test. Depressive symptoms were measured with the Geriatric Depression Scale (GDS) and those with the GDS score being 18 and over were designated as aMCID. By calculating the mean cortical PiB uptake ratio, we divided patients with aMCID into PiB-positive and PiB-negative groups. **Results:** Eight (66.7%) of 12 patients with aMCID were positive for cortical PiB binding. There was a significant difference between PiB-positive and PiB-negative groups in terms of the apolipoprotein E (ApoE) ε4 allele frequency (100% vs. 0%, $p = 0.006$) and GDS score (24.2 vs. 28.2, $p = 0.03$). The neuropsychological assessment revealed that patients with ^{11}C-PiB-negative aMCID performed better on the recognition of visual memory test than those with PiB-positive. **Conclusions:** In patients with aMCID, the presence of cortical amyloid was strongly associated with the APOE ε4 allele. This finding suggests that those with aMCID and ApoE4 genotype may be a prodromal state to AD.

Key Words: *Amyloid imaging, Mild cognitive impairment, Depression*

INTRODUCTION

Mild cognitive impairment (MCI) is a condition that refers to cognitive impairment in subjects without dementia. It is important to identify MCI subjects with prodromal Alzheimer's disease (AD), because if disease-modifying drugs for AD become available, these are likely to benefit the most from the therapy. Although it has been documented that people with MCI have an increased risk of AD [1-5], population-based studies have shown that only one-third develop dementia, whereas others stay on or revert to a normal level of cognitive functioning, suggesting multiple etiologies involved in MCI [6]. Moreover, affective symptoms such as depression, anxiety and apathy are common in subjects with MCI [7], particularly depression. Therefore, when elderly patients have both clinically significant depressive symptoms and cognitive impairment, it is difficult to demonstrate a causal link between depressive symptoms and incident MCI, at least in a shorter

follow-up. At present, the mechanisms by which depression relates to MCI or AD remains unclear. One possibility is that depression and MCI may share the same risk factors such as vascular risk factors, which led to the so called "vascular depression" hypothesis [8]. Underlying ischemic changes within the brain may give rise to neurotransmitter deficits or dysfunction in the frontal-striatal pathway that poses a risk to depression and its associated cognitive symptoms [9]. Another hypothesis is that development of late-life depression symptoms may reflect an underlying neuropathologic condition that will develop also cognitive decline over time. In other words, cognitive impairment along with depressive symptoms may be the early signs of a neurodegenerative disease, particularly AD. Thirdly, MCI related with depression could reflect an underlying psychiatric disorder. This subset often develops a reversible form of dementia, commonly called pseudodementia, or depression with reversible dementia [10]. Even though they are not mutually exclusive, it is important to differentiate those groups in terms of treatment. It would be also interesting to predict among those with amnestic MCI with depression (aMCID) who will exhibit Alzheimer's pathology and progress to AD. Pittsburgh compound B (PiB) is an amyloid PET tracer designed to bind to the fibrillar form of β-amyloid [11-13] and serves as a useful tool for detecting amyloid deposition in the brain in suspected cases .

The primary goal of the current study was to determine what makes those with positive amyloid imaging differentiated from those without in aMCID and investigate whether clinical, neuropsychological and neuroimaging findings help differentiate the two.

MATERIALS AND METHODS

1. Patients

From March 2010 to June 2011, we prospectively recruited new or follow-up patients with amnestic mild cognitive impairment (aMCI) at Asan Medical Center in Seoul, Korea. A sample of 12 individuals were included in this study. They underwent a thorough clinical evaluation and a neurological examination and comprehensive neuropsychological testing. All subjects with MCI fulfilled the following criteria : 1) subjective memory complaints, 2) no dementia diagnosis, 3) activities of daily living intact or functional impairment not due to cognitive impairment, and 4) objective evidence of cognitive impairment. The definition of aMCI was made when the memory measures were below the 16th percentile of the mean for the age, sex and education-matched normal subjects. Depression was initially assessed by means of the Korean version of the 30-item Geriatric Depression Scale (K-GDS [14]). All patients scoring 18 or higher on the K-GDS were screened as depressed. The diagnosis of depressive episodes was reassessed by means of a half-hour structured interview to elicit at least 5 depressive symptoms according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. We excluded patients with other structural lesions on brain MRI such as territorial infarction, intracranial hemorrhage, hydrocephalus, or white matter hyperintensity signal associated with radiation, multiple sclerosis, or vasculitis. Patients completed routine laboratory tests (complete blood counts, blood chemistry profiles, vitamin B_{12}/folate levels, syphilis serology, and thyroid function tests). ApoE genotype using blood specimen was determined. All diagnostic tests were performed 3 months before or after the Pittsburgh Compound B (PiB) PET scan.

1) Control groups for comparison of global PiB uptake ratio

The PiB scans with aMCID were compared with those of two control groups.

2) Normal controls

The normal control group consisted of 10 healthy volunteers (67.3 ± 6.4 years) with no history of neurologic or psychiatric illnesses, and no abnormalities on neurologic examinations. They were family members of outpatients at Memory Disorder Clinic of Asan Medical Center. Their demographic profiles were shown in Table 1.

3) Disease controls (patients with AD)

A total of 14 control patients with AD (71.4 ± 11.7 years) were recruited. The diagnosis of AD was made on the basis of criteria for probable AD proposed by NINCDS-ADRDA [15]. Their demographic profiles were shown also in Table 1.

Table 1. Demographic, clinical, and MRI characteristics of PiB + and PiB – patients

	Total aMCID (n = 12)	PiB+ (n = 8)	PiB- (n = 4)	*p*-value	AD (n = 14)	Normal controls (n = 10)
M : F	1 : 11	1 : 7	0 : 4	> 0.999	7 : 7	2 : 8
Age (yr)	70 ± 8.3	70.8 ± 6.9	68.2 ± 11.7	0.798	71.4 ± 11.7	67.3 ± 6.4
Disease duration (yr)	2.2 ± 0.8	2.4 ± 0.4	1.8 ± 0.8	0.248	5.8 ± 3.0	-
Education (yr)	6.9 ± 4.9	7.2 ± 4.8	6.2 ± 2.0	0.797	10.3 ± 5.8	16.0 ± 1.4
Risk factor, %						
HTN	50	50	50	> 0.999	71.4	20
DM	8.3	25	0	0.333	28.6	15
Hyperlipidemia	25	25	25	> 0.999	42.9	10
Cardiac disease	0	0	0	> 0.999	21.4	0
Smoking	0	0	0	> 0.999	21	0
Previous stroke	0	0	0	> 0.999	14.3	0
Family history	25	37.5	0	0.119	0	0
MMSE	23.5 ± 3.2	22.8 ± 3.6	25.0 ± 5.6	0.265	16.8 ± 5.0	29.0 ± 0.8
CDR	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	> 0.999		
CDR SB	1.5 ± 0.4	1.5 ± 0.5	1.3 ± 0.4	0.521		
GDS	25.5 ± 3.0	24.2 ± 2.4	28.2 ± 2.2	0.030*		
HIS	1.6 ± 1.1	1.3 ± 1.0	2.2 ± 1.2	0.286		
S-IADL	5.3 ± 4.3	6.8 ± 4.5	2.2 ± 1.8	0.119		
NPI	6.3 ± 6.2	5.0 ± 6.9	9.0 ± 3.5	0.123		
DSM-IV	6.7 ± 1.1	6.5 ± 1.4	7.2 ± 0.5	0.221		
Number of lacunes†	0	0	0	> 0.999		
Number of MB‡	0.4 ± 1.26	0.5 ± 1.5	0.0 ± 0.0	> 0.999		
APOE ε4 allele, %						
0 (-/-)	33.3	0.0	100.0			
1 (-/+)	50.0	75.0	0.0	0.002*		
2 (+/+)	16.7	25.0	0.0			
MTA left	1.7 ± 1.4	1.75 ± 1.4	2.0 ± 1.4	0.748		
MTA right	1.9 ± 1.3	1.75 ± 1.4	2.2 ± 1.2	0.685		
WMLV† (mL), median (IQR)	2,014, (220-14,695)	583, (220-14,695)	2,430, (2,014-6,378)	0.307		

*$p < 0.05$; †lacunes and WMLV were evaluated in 11 patients because a patient had only T2-weighted image; ‡MB was rated in 9 patients because 3 patients did not have FEF image.

aMCID, amnestic mild cognitive impairment with depression; CDR, Clinical Dementia Rating; DM, Diabetes mellitus; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; GDS, Geriatric Depression Scale; HIS, Hachinski Ischemic Scale; HTN, hypertension; IQR, interquartile range; MB, microbleeds; MMSE, Mini-Mental State Examination; MTA, medial temporal atrophy; NPI, Neuropsychiatric inventory; PiB, Pittsburgh compound B; SB, sum of boxes; S-IADL, Seoul-Instrumental activities of daily living; WMLV, white matter lesion volume.

4) Standard protocol approvals, registrations, and patient consents

We obtained written consents from each participant and the Institutional Review Board of Asan Medical Center approved the study protocol.

2. Neuropsychological tests

All patients underwent neuropsychological tests using a standardized battery called the Seoul Neuropsychological Screening Battery [16]. This Battery assess attention, language, praxis, elements of Gerstmann syndrome, visuospatial/constructive function, verbal and visual memory, and frontal/executive function.

3. Brain MRI

1) MRI acquisition

Nine patients were scanned at Asan medical center for MRI, which were acquired via 5 different techniques (i.e., 3-dimensional T1 turbo field echo [240 × 240 field of view, voxel size $0.5 \times 0.5 \times 0.5$ mm^3, TE 3.7ms, TR 10.0 ms, slice thickness 4mm], fluid-attenuated inversion recovery, T1, T2, and fast field echo) using identical imaging protocols on a 1.5-T MRI scanner (Achieva, Philips 1.5 T, Eindhoven, Netherlands). The remaining three patients had limited MRI sequences. Two

patients did not have fast field echo and one patient had only T2 weighted MRI scan. Due to the lack of image sequences, we excluded one patient for lacune counts and WML volume, and three patients for microbleeds for our analyses.

2) Rating of lacunes and microbleeds on MRI

Two neurologists blinded to clinical information counted the total number of lacunes and microbleeds. Lacunar infarction was defined as a small lesion less than 15 mm in diameter with a low signal on T1-weighted images, a high signal on T2-weighted images, and a perilesional halo on FLAIR images [17]. A microbleed was defined as a homogeneous round signal loss lesion with a diameter ≤ 10 mm on the FEE image [17]. Intrarater correlations were obtained by the same rater with a 3-month interval between ratings.

3) Visual rating of medial temporal lobe atrophy on MRI

Medial temporal lobe atrophy (MTA) was assessed visually [18] by 2 neurologists who were blinded to the diagnosis and age of the subjects after a series of training sessions. The T1 coronal images were used for the visual assessment and left and right MTA were rated separately. The degree of MTA was rated from 0 (no atrophy) to 4 (severe atrophy). Intrarater correlations were measured at the same interval as described above.

4) Image Analysis of white matter volume

We used the ANALYZE software package (Mayo Clinic, USA), version 10.0 to process images and estimate the volume of the white matter lesion (WML). Due to different slice thickness of each FLAIR images, we resampled the original FLAIR images with slice thickness 4 mm using the ANALYZE software. After resampling, we used the region-of-interest (ROI) function within the package, which could allow the rater to create automated traces along with WML on individual images. When the largest diameter of WML were adjacent to the ventricular lining (such as adjacent to the occipital and frontal horns, and the lateral ventricles), it was considered periventricular WML and otherwise, they were considered as subcortical WMLs. In order to obtain the volume, ROI area was multiplied to slice thickness (4 mm). ROI volumes from the entire images were then summed to calculate a total volume in cubic milliliter. All summation process was performed automatically in the ANALYZE program.

4. ^{11}C-PIB PET

All patients were examined at the Asan medical Center using identical image parameters and PET scanncer.

1) Radiochemistry

The specific radioactivity of ^{11}C-PiB at the time of administration was more than 1,500 Ci/mmol for patients and the radiochemistrical yield was more than 35%. The radiochemical purity of the tracer was more than 95% in all PET studies.

2) Scanning protocol

All subjects underwent a PET scan using a Discovery Ste PET/CT scanner (GE Medical Systems, Milwaukee, WI) in a 3 dimensional scanning mode that examined 35 slices of 4.25-mm thickness that spanned the entire brain. The ^{11}C-PiB was injected into an antecubital vein as a bolus with a mean dose MBq (i.e., range 259-550 MBq). A CT scan was performed for attenuation correction at 60 minutes after the injection. A 30-minute emission static PET scan was the initiated.

3) Data analysis

The cerebellum was used as a reference region for analysis. Ratio parametric images representing ^{11}C-PiB uptake in each voxel were created to determine the region-to-cerebellum ratio of radioactivity.

(1) Statistical parametric mapping analysis

A voxel-based statistical analysis was performed using the Statistical Parametric Mapping program, version 2 (SPM; Wellcome Department of Imaging Neuroscience, University College London, UK), and Matlab 6.5 for Windows (Mathworks, Natick, MA). Spatial normalization of the ratio parametric images of ^{11}C-PiB was performed using a coregistered MRI.

(2) Automated region of interest analysis

We compared PiB retention in global cortices and regions of interests (ROIs) among groups by calculating the cortical PiB uptake ratio in an anatomically defined ROI. The global cortical PiB uptake ratio was determined by combining the

bilateral frontal, parietal, temporal and occipital cortices, and posterior cingulate gyrus.

4) PiB-positive vs PiB-negative

To differentiate between PiB-negative (PiB-) and PiB-positive (PiB+), we used the global PiB uptake as described earlier [19]. In brief, patients in aMCID were classified as PiB+ or PiB - according to measured global PiB uptake ratio values. Patients were considered PiB+ if their global PiB uptake value was more than 2 standard deviations of the mean of the normal controls.

5. Statistical analyses

All statistical analysis was performed using SPSS for Windows version 18.0 (Windows, Chicago, Illinois, USA). Descriptive statistics of the initial workup were performed using demographics and clinical scores from neuropsychological tests. Mann-Whitney test were used to assess continuous variables and Fisher's Exact test to assess dichotomous variables. Interrater and intrarater reliability were examined using the κ statistic with regards to visual ratings of MTA, and intraclass correlation coefficient analysis with regards to counting lacunes, microbleeds and WML volume. Statistical significance was defined as $p < 0.05$.

RESULTS

1. Interrater/intrarater reliability of lacune/microbleed, visual ratings of MTA and intraclass correlation coefficient of WML volume

The intrarater correlation coefficient was 1.000 ($p < 0.001$) for lacune counts and 1.000 ($p < 0.001$) for microbleeds, reflecting a high level of correlation. The interrater reliabilities for lacune and microbleed counts were also high, 1.000 ($p < 0.001$) and 0.999 ($p < 0.0001$), respectively. In addition, the intrarater reliability for visual ratings of MTA was 0.575-0.673 (κ, $p < 0.001$), which also revealed very high comparability. The interrater reliability of MTA was not calculated due to the differences of ratings for raters, which was caused by small sample size. The intraclass correlation coefficient of WML volume was 0.998 ($p < 0.001$).

2. Frequency of aMCID with PiB+ vs PiB-

A total of 8 (66.7%) of the 12 patients tested positive for PiB retention, while 4 (33.3%) tested negative for PiB retention.

3. Demographic, clinical, and MRI characteristics of patients with PiB+ vs PiB- aMCID

Table 1 showed the demographic characteristics and MRI variables of patients with PiB+ and PiB- aMCID. There were significant differences between the two groups in terms of GDS and ApoE4 allele frequency. Patients with PiB+ aMCID had a lower score in GDS ($p < 0.03$) and carried higher frequency of the ApoE4 allele ($p < 0.002$). There were no significant differences between the two groups with regards to age, gender, vascular risk factors, MMSE, CDR, S-IADL, NPI and MRI variables (number of lacunes, number of microbleeds, WML volume and the degree of MTA). Fig. 1 shows the representative MRI findings (presence of lacunes, microbleeds, WML and MTA) and PET images. Not a single lacune on MRI scans was observed in all subjects. There were no significant differences in the number of microbleeds and severity of MTA between the two groups.

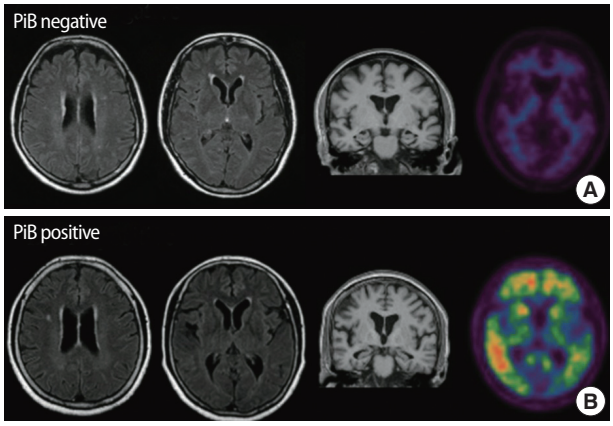

Fig. 1. Representative cases of Pittsburg compound B (PiB) PET. (A) PIB-negative mild cognitive impairment with depression (MCID) vs (B) PiB-positive MCID.

Table 2. Neuropsychological function of PiB + and PiB – patients

Neuropsychological tests	Total (n = 12)	PiB + (n = 8)	PiB – (n = 4)	*p*-value
Attention				
Digit span forward	5.6 ± 1.2	5.5 ± 1.4	6.0 ± 1.6	0.585
Digit span backward	3.0 ± 0.6	5.5 ± 1.4	3.2 ± 0.96	0.503
Language and related functions				
K-BNT	37.0 ± 10.9	37.0 ± 12.4	37.0 ± 8.7	0.799
Calculation	10.0 ± 2.9	5.5 ± 1.4	9.5 ± 3.7	0.856
Visuospatial funtction				
RCFT	29.3 ± 6.8	30.1 ± 5.2	27.7 ± 10.1	0.864
Memory				
SVLT immediate recall	12.0 ± 5.7	11.3 ± 3.0	13.2 ± 9.7	0.670
SVLT delayed recall	1.7 ± 2.7	0.7 ± 1.4	3.7 ± 3.8	0.087
SVLT recognition	9.8 ± 3.1	9.8 ± 3.8	9.7 ± 1.7	0.415
RCFT immediate recall	8.4 ± 6.5	6.8 ± 6.0	11.5 ± 7.1	0.306
RCFT delayed recall	6.7 ± 6.5	4.6 ± 5.9	11.1 ± 6.1	0.147
RCFT recognition	17.7 ± 2.3	16.7 ± 2.2	19.7 ± 0.9	0.032*
Frontal/executive function				
COWAT animals	10.6 ± 3.3	11.0 ± 3.6	10.0 ± 3.1	0.864
COWAT supermarket	11.2 ± 6.1	10.5 ± 6.9	12.7 ± 4.6	0.395
Phonemic fluency	18.6 ± 7.0	19.8 ± 8.0	16.5 ± 5.0	0.704
Stroop test letter reading	98.8 ± 22.7	94.0 ± 26.6	108.5 ± 6.35	0.650
Stroop test color reading	60.4 ± 26.2	55.1 ± 28.3	74.6 ± 14.0	0.221

Values are presented as mean ± SD.
*$p < 0.05$.
COWAT, Controlled Oral Word Association test; K-BNT, Korean version of the Boston Naming Test; PiB, Pittsburgh compound B; RCFT, Rey-Osterrieth Complex Figure Test; SVLT, Seoul Verbal Learning Test.

4. Neuropsychological performance of patients with PiB+ and PiB- aMCID

Subjects' scores on the neuropsychologic test battery were presented in Table 2. PiB+ group tended to show lower performance not only on Rey Complex Figures test (RCFT) recognition part, but also on Seoul Verbal Learning Test delayed recall, RCFT immediate recall, and RCFT delayed recall tests, although statistical significance was not reached except the recognition part of RCFT.

5. Quantitative analysis for PiB retention in patients with aMCID

A quantitative analysis of ^{11}C-PiB PET revealed that patients with PiB+ aMCID exhibited a higher PiB uptake ratio of the frontal, parietal, temporal, occipital and posterior cingulate cortices to cerebellum than that of the PiB-aMCID group. The mean cortical uptake ratio of patients with PiB+ aMCID was as high as that of patients with AD, whereas the average uptake ratio of patients with PiB-aMCID was similar to that of normal controls (Fig. 2).

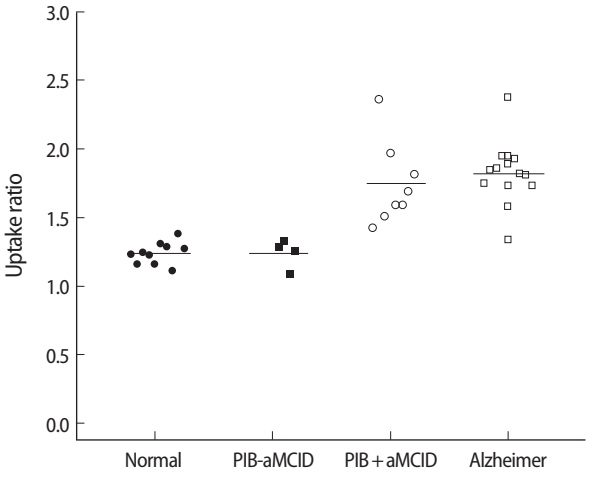

Fig. 2. Scatterplots of the global Pittsburgh compound B (PIB) uptake ratio for normal controls, amnestic MCI with depression, and Alzheimer disease. The mean uptake ratio of patients with PiB+ aMCID was as high as that of patients with Alzheimer disease, whereas the average uptake ratio of patients with PiB- aMCID was similar to that of normal controls. aMCID = amnestic mild cognitive impairment with depression.

DISCUSSION

The primary goal of this study was to investigate differences between patients with PiB- and PiB+ aMCID in terms of clinical, neuropsychological, and MRI profiles. The PiB- and PiB+ groups did not differ with regards to age, vascular risk factors and MRI profiles including white matter volume, the number of lacune, microbleeds and the degree of MTA. The two variables that stood out as significant for PiB positivity were the presence of the APOE4 allele and GDS. ApoE4 is an established genetic risk factor for late-onset AD based on numerous studies of various ethnicities and populations [20]. Moreover, ApoE4 is associated with cognitive decline in the elderly with normal cognition [21]. The possible mechanism by which ApoE4 increased the risk for cognitive impairment and dementia is that ApoE4 accelerated the deposition of the beta amyloid in the brain [22]. Another plausible mechanism would be that ApoE4 had a modifiable effect on the association between atherosclerosis and cognitive decline [23], even though, in our study, there were no statistically significant dif-

ferences in cerebrovascular risk factors and ischemic lesions between the two groups. One could postulate that a synergistic or complementary interaction between ApoE4 and depression may have contributed to the development of amyloid pathology and cognitive decline. The present study suggests that there may be at least two depression subtypes in the elderly patients with aMCI: (1) amyloid-associated depression (PiB + group : more likely to be a prodromal stage of AD), and (2) nonamyloid-associated depression (PiB- group: related to vascular depression, pseudomentia or psychiatric disorders).

There was also a statistically significant difference in terms of GDS between the two groups. Patients with PiB- aMCID had a higher depression score than PiB+ group (28.2 ± 2.2 vs 24.2 ± 2.4). Depression should be more severe to cause the same degree of cognitive impairment in aMCID subjects without amyloid pathology. Our results suggested that in the PiB- aMCID, depression per se may be the primary cause of cognitive impairment. Depression-associated hypercortisolemia may promote hippocampal atrophy and reduced connectivity leading to learning/episodic memory impairment [24].This subset of aMCID may develop a reversible from of cognitive impairment, which is not linked to the Alzheimer's pathology.

The strength of current study is that we identified individuals with aMCID who have amyloid deposition in the brain and consequently are at an increased risk of developing AD using *in vivo* molecular imaging.

Our study has several limitations. First, the sample size was too small to reliably detect any significant differences other than ApoE4 between PiB- and PiB+ groups. However, no studies have yet been performed to predict the presence of amyloid pathology in the brain and to determine the predisposing factors. Thus, the current study could serve as a pilot study in elucidating the association of depression with cognitive impairment and dementia. Second, we did not collect information about treatments for depression and the responsiveness to antidepressants. Third, given that our subjects consisted of 11 women and 1 man, we should take into account the possible impact of selection bias on the gender difference, when interpreting the results. In a few studies [25, 26], depression was significantly associated with dementia only in men [25, 26], whereas most other studies found no gender differences [27]. Another limitation is that the study population was not representative of MCID patients. Indeed, it comprised only aMCI patients. According to the recent study [28] of different MCI subtypes, the proportion of amyloid positivity was different among the MCI subtypes. Future study is warranted to include various subtypes of MCI to identify which type is more associated with amyloid deposition and what are the clinical or radiological factors predictive of the involvement of Alzheimer's pathology in those with MCID.

It is clinically important and challenging to determine whether depression is a true risk factor or an early manifestation of AD. Our findings suggest that patients with aMCID may have a good chance of having cortical amyloid deposition and possibly the prodromal state to AD if they are an ApoE4 carrier and/or a moderately depressive individual. Caution should be exercised in drawing a conclusion that depression is strongly associated with Alzheimer's pathology. Since we did not include subjects without depression, we cannot decisively relate depression to an increased risk of AD. Elderly people with both ApoE4 allele and moderate depression should be monitored more carefully for the development of AD. Given the unmodifiable nature of genetic factors and the overall good response of depression to pharmacological and psychological management, depression should be treated appropriately in the timely manner for those with both risk factors. Prospective longitudinal study is imperative to further explore the prognostic implications of positive amyloid imaging in individuals with MCI and depression.

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