A 4-Year Follow-Up of Subjects with Visually Equivocal Amyloid Positron Emission Tomography Findings from the Alzheimer's Disease Neuroimaging Initiative Cohort

Minyoung Oh[1] · Minjung Seo[2] · Sun Young Oh[3] · Heeyoung Kim[4] · Byung Wook Choi[5] · Jungsu S. Oh[1] ·
Jae Seung Kim[1] (ORCID) · for the Alzheimer's Disease Neuroimaging Initiative

Abstract

Background To date, the clinical significance of visually equivocal amyloid positron emission tomography (PET) has not been well established.

Objective We studied the clinical significance of equivocal amyloid PET images from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods Subjects with F-18 florbetapir PET scans at baseline who were followed up for 4 years were selected. Clinical characteristics, imaging biomarkers, cognitive function, and rate of conversion to AD were compared in subjects with visually equivocal findings.

Results Of 249 subjects who completed the follow-up, 153 (61.4%), 20 (8.0%), and 129 (30.5%) were F-18 florbetapir-negative, -equivocal, and -positive, respectively. The mean standardized uptake value ratios (SUVR) of F-18 florbetapir PET were 0.75 ± 0.04, 0.85 ± 0.10, and 1.00 ± 0.09 for each group ($p < 0.001$ between groups), and 15.0%, 70.0%, and 98.7% of patients were quantitatively above the positive threshold. The change in the SUVR of F-18 florbetapir PET was higher in the equivocal ($6.09 \pm 3.61\%$, $p < 0.001$) and positive ($3.13 \pm 4.38\%$, $p < 0.001$) groups than the negative group ($0.88 \pm 4.28\%$). Among the subjects with normal or subjective memory impairment and mild cognitive impairment, 5.3% with negative amyloid PET and 37.5% with positive amyloid PET converted to AD over the 4-year period. None of the equivocal amyloid PET subjects converted to AD during this period.

✉ Jae Seung Kim
  jaeskim@amc.seoul.kr

  Minyoung Oh
  my@amc.seoul.kr

  Minjung Seo
  minjungseo@naver.com

  Sun Young Oh
  clare.sy.o@gmail.com

  Heeyoung Kim
  nmkimh@gmail.com

  Byung Wook Choi
  nmchoibw@gmail.com

  Jungsu S. Oh
  jungsu.oh@gmail.com

[1] Department of Nuclear Medicine, Asan Medical Center, Seoul, Korea

[2] Department of Nuclear Medicine, Ulsan University Hospital, Ulsan, Korea

[3] Department of Nuclear Medicine, National Police Hospital, Seoul, Korea

[4] Department of Nuclear Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea

[5] Department of Nuclear Medicine, Daegu Catholic University Medical Center, Daegu, Korea

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Conclusion Approximately 8% of subjects from the ADNI cohort showed visually equivocal amyloid PET scans with intermediate load and rapid accumulation of amyloid, but did not convert to AD during the 4-year follow-up.

Keywords Amyloid · Positron-emission tomography · Alzheimer disease · Cognitive dysfunction

Introduction

Alzheimer's disease (AD) was initially defined as a clinical-pathologic entity and diagnosed as possible or probable AD using clinical criteria, including insidious onset and progressive impairment of memory and other cognitive functions. A definite diagnosis was provided following demonstration of plaques and tangles by autopsy [1]. However, postmortem validation of people clinically diagnosed with probable AD was shown to be diverse in relation to pathologic AD, tangle-only dementia, dementia with Lewy bodies, mixed AD, vascular dementia, and frontotemporal dementia [2]. This finding indicates that clinical diagnosis of AD is not an etiology, but rather the clinical consequences of one or more diseases. This made enrollment of patients with non-AD pathology in clinical trials that testing disease-modifying interventions for biologically defined targets [3]. Therefore, the need for biological diagnostic criteria has been raised and proposed as the National Institute on Aging and Alzheimer's Association (NIA-AA) research framework [4]. This framework defines AD biologically by neuropathologic changes or biomarkers, which in turn provide a common language for researchers. However, it also raises questions regarding the definition of biomarker positivity. For amyloid-β (Aβ) peptides, there are several tracers for positron emission tomography (PET) that provide specific criteria for binary visual reading [5–7]. However, some patients showed visually equivocal PET findings, which commonly represent intermediate amyloid load; nevertheless, clinical follow-up to assess cognitive evolution in subjects with equivocal scans was needed [8–11]. We previously reported the clinical significance of patients with equivocal amyloid PET at the 2-year follow-up using the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort [12]. In this study, the results of 4 years of longitudinal observations have been reported.

Materials and Methods

Participants

We included subjects with cognitively normal (NC) or subjective memory impairment (SMI), mild cognitive impairment (MCI), and AD who had F-18 florbetapir PET scans at baseline and were followed up (F/U) for 4 years as of June 2017 as a part of the ADNI study. The criteria for classification of the subjects were described previously [13]. The ADNI study was approved by the Institutional Review Board of the respective institutions before beginning the study. Informed consent was obtained from all participants. The results of the 24-month follow-up have been reported previously [12]. All ADNI data are publicly available at http://www.loni.ucla.edu/ADNI.

F-18 Florbetapir PET Image Processing

ADNI PET image data were acquired as described online (adni.loni.ucla.edu/about-data-samples/image-data/) and processed as described previously [14]. Briefly, F-18 florbetapir PET image data were co-registered with 3T 3D MP-RAGE magnetic resonance imaging (MRI) and segmented and parcellated into individual cortical regions using FreeSurfer. The mean florbetapir uptake was extracted from the gray matter within the lateral and medial frontal anterior, posterior cingulate, lateral parietal, and lateral temporal regions. The standardized uptake value ratio (SUVR) relative to uptake in the composite region comprising the whole cerebellum and pons, with the eroded subcortical white matter as the reference region [15] and a positivity threshold of 0.79, was described previously. This ratio provides more accurate and conservative change measurements [15, 16]. The full protocols and data are available online (http://adni.loni.ucs.edu).

We conducted harmonization of different PET scanners to achieve the best visual analysis. Detailed descriptions of image processing and analysis have been reported in the previous study [12]. A panel of five independent board-certified nuclear medicine physicians that were blinded to all clinical information assessed all F-18 florbetapir PET images. Scans were considered 1 if there was some significant F-18 florbetapir cortical retention and 0 if there was no significant cortical retention according to previously defined criteria [17]. And the results were classified into three categories as follows: positive scan, if more than four observers rated the scan as 1; negative scan, if more than four observers rated the scan as 0; and equivocal scan, if there were no more than four observers with the same ratings.

F-18 Fluorodeoxyglucose (FDG) PET Image Processing

Each F-18 FDG PET image was spatially normalized to the standard O-15 H$_2$O PET template using Statistical Parametric Mapping software (SPM5, Wellcome Department of Cognitive Neurology, UK; www.fil.ion.ucl.ac.uk/spm). The

mean FDG uptake was extracted for each participant from a set of study-independent and previously validated regions of interest (metaROIs) located in the right and left inferior temporal and lateral parietal regions, and a bilateral posterior cingulate cortex region relative to the mean of the pons and cerebellar vermis reference regions [18].

Structural MRI Analyses

Cross-sectional structural differences were assessed using hippocampal volumes defined on MPRAGE images by FreeSurfer v5.1 and were divided by the total intracranial volume to adjust for head size.

Cerebrospinal Fluid (CSF) Analysis

CSF $A\beta_{1-42}$ was concurrently measured using F-18 florbetapir scans at baseline and analyzed at the ADNI Biomarker core laboratory. We applied the autopsy-validated CSF $A\beta_{1-42}$ positivity cut-off of 192 pg/mL, which was utilized in a previous study [19].

Clinical and Cognitive Measurements

We examined several clinical and cognitive performance measurements, including baseline and longitudinal performance, using the Mini-Mental State Examination (MMSE) [20], Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) [21], and clinical dementia rating-sum of boxes (CDR-SB) [22]. We also examined clinical profiles, including clinical diagnosis at baseline and 48-month F/U, to decide whether conversion to AD occurred during the F/U.

Statistical Analysis

Chi-squared test was used for categorical variables, and one-way analysis of variance for quantitative variables. P-values were two-sided and considered statistically significant at < 0.05 for global comparison and at < 0.05/3 for subgroup analyses to take into account multiple comparisons. Inter-observer agreement of the visual assessment was calculated on subject level using kappa values. Analyses were performed using SPSS® software (Statistical Package for the Social Science, version 18.0, Chicago, IL, USA).

Results

Demographic and Clinical Characteristics

The demographics, clinical characteristics, and biomarker variables are summarized in Table 1. Among 249 subjects who completed the 4-year follow-up, the mean age of the patients

was 71.6 ± 6.9 years, and 53.0% were men. The mean number of years of formal education was 16.5 ± 2.5 years. The numbers of F-18 florbetapir negative/equivocal/positive subjects were 153 (61.4%), 20 (8.0%), and 129 (30.5%), respectively. A total of 8% of subjects with NC or SMI ($n = 8/100$), 8.4% of patients with MCI ($n = 12/143$), and no patients with AD ($n = 0/6$) showed equivocal F-18 florbetapir PET findings. Among the 20 subjects in the equivocal group, 9 (45.0%) showed diffuse mild amyloid retention in the entire cerebral cortex. Among the remaining patients, retention was most common in the frontal cortex ($n = 5$, 20.0%), followed by the posterior cingulate gyrus ($n = 3$, 15.0%), temporal cortex ($n = 2$, 10.0%), and occipital cortex ($n = 1$, 5.0%). The types of equivocal F-18 florbetapir PET images are shown in Fig. 1. Among subjects with NC/SMI or MCI, 5.3% of subjects with negative amyloid PET and 37.5% of subjects with positive amyloid PET converted to AD during the 4-year follow-up. None of the subjects with equivocal amyloid PET converted to AD during the 4 years.

Biomarkers

At baseline, 32 (20.9%), 10 (50.0%), and 58 (76.4%) subjects with negative/equivocal/positive F-18 florbetapir PET were apolipoprotein E4 (ApoE4) positive. The mean SUVR of F-18 florbetapir PET was 0.75 ± 0.04, 0.85 ± 0.10, and 1.00 ± 0.09 for each group ($p < 0.001$ between groups). Among them, 15.0%, 70.0%, and 98.7% of the patients in each group were quantitatively above the positive threshold. The metaROI of FDG was significantly more hypometabolic in the positive group than those in the equivocal or negative groups ($p = 0.010$ and $p < 0.001$, respectively). Furthermore, the hippocampal volume normalized to the intracranial volume of the positive group was significantly lower than that of the negative group ($p < 0.001$). The CSF $A\beta_{1-42}$ level was significantly lower in the positive group (133.43 ± 24.02) than that in the negative group (215.38 ± 38.56, $p < 0.001$), but was not significantly different to that in the equivocal group (174.24 ± 43.73, $p = 0.270$). Moreover, the CSF $A\beta_{1-42}$ level was quantitatively positive in 35 (26.1%), 12 (70.6%), and 70 (97.2%) subjects in each group.

The changes in the SUVR of F-18 florbetapir PET were higher in the equivocal ($6.09 \pm 3.61\%$, $p < 0.001$) and positive ($3.13 \pm 4.38\%$, $p < 0.001$) groups than that in the negative group ($0.88 \pm 4.28\%$). Subject-specific time trajectories of amyloid burden measured by the SUVR of F-18 florbetapir PET in subjects with CN or SMI (Fig. 2a) and MCI (Fig. 2b) were presented. Changes in the SUVR, FDG metaROI, and hippocampal volume normalized to intracranial volume in each group during follow-up are shown in Table 1 and Fig. 3a–c.

Table 1 Demographics and clinical and biomarker variables of subjects with negative/equivocal/positive F-18 florbetapir PET images

	Negative ($n = 153$)	Equivocal ($n = 20$)	Positive ($n = 76$)
Demographics			
Age (y) [a]	70.6 ± 7.1	73.1 ± 6.3	73.0 ± 6.5
Sex, M/F (n)	82: 71	9: 11	41: 35
Education (y)	16.6 ± 2.4	17.2 ± 2.4	16.0 ± 2.7
Clinical diagnosis			
NC + SMI (total $n = 100$; n, %) [a]	74 (74.0%)	8 (8.0%)	18 (18.0%)
MCI (total $n = 143$; n, %) [a]	77 (53.8%)	12 (8.4%)	54 (37.8%)
AD (total $n = 6$; n, %) [a]	2 (33.3%)	0 (0.0%)	4 (66.6%)
Conversion to AD			
Conversion to AD until 2-year F/U (n, %) [a]	5 (3.3%)	0 (0.0%)	20 (27.8%)
Conversion to AD until 4-year F/U (n, %) [a]	8 (5.3%)	0 (0.0%)	27 (37.5%)
Biomarkers			
ApoE4 + (n, %) [a]	32 (20.9%)	10 (50.0%)	58 (76.4%)
F-18 Florbetapir (SUVR) [a]	0.75 ± 0.04 [c, d]	0.85 ± 0.10 [b, d]	1.00 ± 0.09 [b, c]
F-18 Florbetapir (SUVR) + (n, %) [a]	23 (15.0%)	14 (70.0%)	75 (98.7%)
FDG metaROI [a]	1.32 ± 0.11	1.31 ± 0.13 [c]	1.22 ± 0.13 [b, c]
Hippocampal volume/ICV (%) [a]	0.50 ± 0.07	0.48 ± 0.06	0.45 ± 0.07 [b]
CSF Aβ_{1-42} (pg/ml) [a]	215.38 ± 38.56	174.24 ± 43.73	133.43 ± 24.02 [b]
CSF Aβ_{1-42}, + (n, %) [a]	35 (26.1%)	12 (70.6%)	70 (97.2%)
Biomarkers (changes over 24 or 48 months)			
F-18 Florbetapir, % (48 months-baseline) [a]	0.88 ± 4.28 [c, d]	6.09 ± 3.61 [b]	3.13 ± 4.38 [b]
FDG metaROI, % (baseline-24 months) [a]	0.52 ± 4.36 [d]	3.92 ± 3.05	3.56 ± 6.15 [b]
Hippocampus/ICV, % (baseline-48 months) [a]	5.14 ± 4.78 [d]	6.51 ± 5.65	14.45 ± 7.68 [b]
Cognitive function			
MMSE (score) [a]	28.6 ± 1.6 [d]	27.8 ± 1.9	27.7 ± 2.2 [b]
ADAS-cog (score) [a]	10.7 ± 5.4 [d]	13.6 ± 5.5	16.8 ± 8.1 [b]
CDR-SB (score) [a]	0.7 ± 1.0 [d]	0.8 ± 0.9	1.5 ± 1.3 [b]
Cognitive function (changes over 48 months)			
MMSE (baseline-48 months) [a]	0.3 ± 1.9 [d]	-0.7 ± 2.0 [d]	3.7 ± 4.4 [b, c]
ADAS-cog (48 months-baseline) [a]	0.2 ± 4.7 [d]	-0.3 ± 5.7 [d]	7.9 ± 11.4 [b, c]
CDR-SB (48 months-baseline) [a]	0.1 ± 1.2 [d]	-0.1 ± 0.6 [d]	2.7 ± 4.0 [b, c]

Mean (SD) shown for continuous variables and proportion positive/abnormal shown for dichotomous variables

ApoE apolipoprotein E, *metaROI* previously validated region of interest, *ICV* intracranial volume, *MMSE* Mini-Mental State Examination, *ADAS-cog* Alzheimer's Disease Assessment Scale-cognitive subscale, *CDR-SB* clinical dementia rating-sum of boxes

$p < 0.05$ for comparison among three groups: a

$p < 0.016$ compared to negative: b, equivocal: c, or positive: d groups

Cognitive Function

The mean MMSE score at baseline in the positive group (27.7 ± 2.2) was lower than that in the negative group (28.6 ± 1.6, $p = 0.001$), and not significantly different in the equivocal group (27.8 ± 1.9, $p = 1.000$). Moreover, the MMSE score decreased significantly in the positive group compared with the other groups during the 4-year follow-up ($p < 0.001$). The baseline ADAS-cog score in the positive group (16.8 ± 8.1) was higher than that in the negative group (10.7 ± 5.4, $p < 0.001$) and not significantly different from that in the equivocal group (13.6 ± 5.5, $p = 0.129$). In addition, the ADAS-cog score increased significantly in the positive group during the 4-year follow-up ($p < 0.001$), as did the CDR-SB score. The changes in MMSE and ADAS-cog and CDR-SB scores in each group during follow-up are shown in Fig. 3d–f.

Discussion

The current study followed subjects from the ADNI cohort with visually equivocal amyloid PET findings for 4 years. We previously reported that the subjects showed intermediate
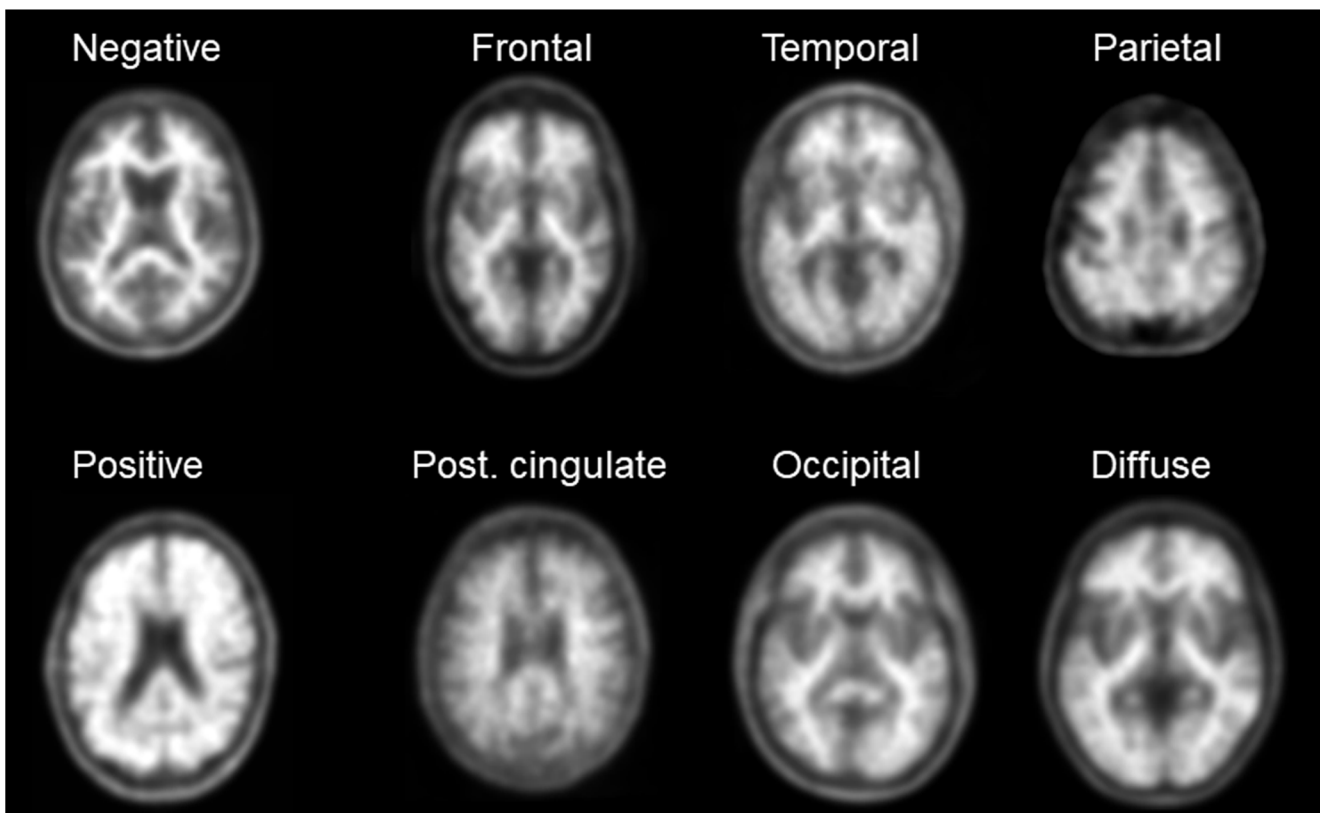
Fig. 1 Visually equivocal F-18 florbetapir PET images

amyloid load at baseline and rapid accumulation during the 2-year follow-up [12]. After the 4-year follow-up, changes of imaging biomarkers, including the degree of hypometabolism on FDG PET and hippocampal volume in MRI, were not significantly different, did not deteriorate cognitively, and did not convert to AD.

Two main neuropathologic hallmarks of AD are amyloid plaques and neurofibrillary tangles [23, 24]. It is considered to occur about 15 years prior to the onset of clinical symptoms of AD [25], Aβ peptides converted to β-sheet-enriched structures [26]. β-sheet structures aggregate into forms of toxic soluble oligomers, seeds, and, eventually, amyloid plaques, which related neurodegeneration in AD [27]. Therefore, Aβ accumulation in the brain is considered to be a spectrum.

Amyloid PET scans are rated as either positive or negative in clinical practice; however, equivocal ratings are often found in some patients. Although the definitions of equivocal amyloid PET vary in the respect of inter-rater agreement or degree of cortical retention, it has been known as intermediate amyloid load in previous reports, regardless of the type of tracers
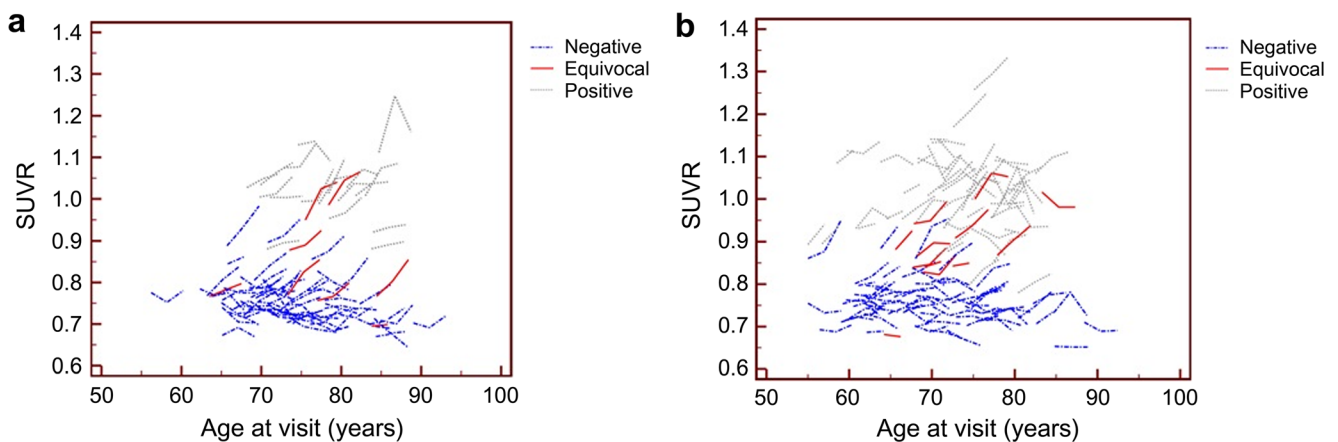
Fig. 2 Changes in SUVR standardized uptake value ratio in cognitively normal subjects (a) and patients with mild cognitive impairment (b) with negative/equivocal/positive F-18 florbetapir PET findings
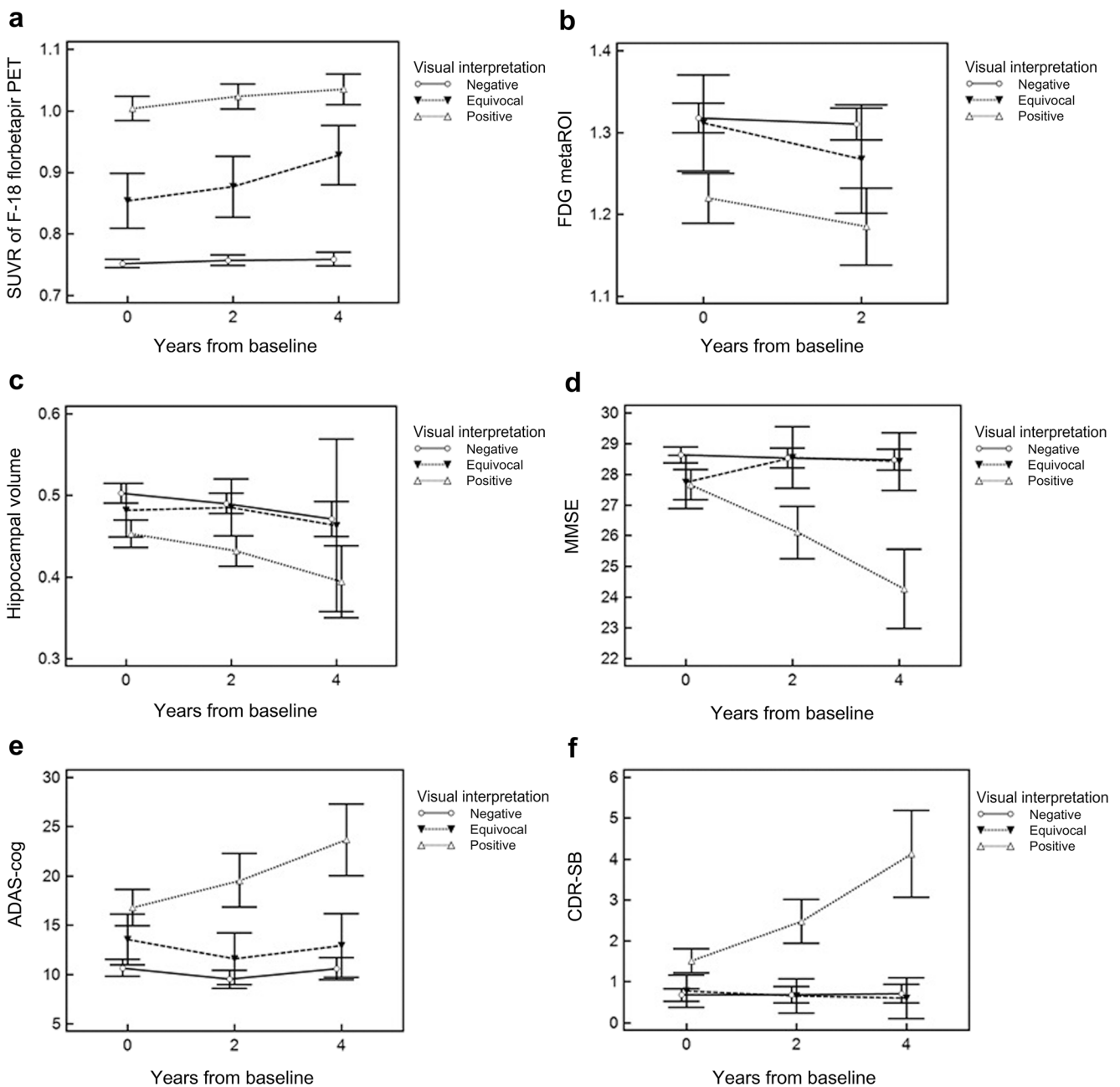
Fig. 3 Changes in SUVR (**a**), FDG metaROI (**b**), hippocampal volume normalized by intracranial volume (**c**), MMSE (**d**), ADAS-cog (**e**), and CDR-SB (**f**) in subjects with visually negative/equivocal/positive amyloid PET

used [10, 15, 28–31]. Equivocal amyloid PET was first described by Hosokawa et al., as a quantitatively intermediate amyloid load, both regionally and globally, observed using C-11 Pittsburgh compound B (PIB). When the first F-18-labeled amyloid PET tracer, F-18 florbetapir was introduced, the FDA withheld approval until an interpretation training program was implemented to reduce inter-reader variability [32]. A portion of equivocal findings continue to be observed even after the approval for clinical use of F-18-labeled amyloid PET tracers, including F-18 florbetapir, F-18 flutemetamol, and F-18 florbetaben, which led to the development of special

educational reading programs that improved inter-rater agreement in the early 2010s [33]. It could be a fundamental problem of F-18 amyloid PET tracers due to the higher white matter retention of F-18-labeled amyloid PET tracers than C-11 PIB [34], since almost all visual interpretation criteria is to determine whether the relative cortical uptake is increased in comparison to white matter retention.

It has been demonstrated that quantitative analysis using the SUVR of static images can reduce inter-rater variability and improve accuracy [30, 35]. To avoid individual variation in white matter retention of static images that acquire the recommended

time frame, analysis of parametric images with dynamic acquisition has also been reported and shows overestimation of cortical uptake in static images [9]. Although these methods of quantitative analysis obviously compensate for the shortcomings of visual interpretation, they are disadvantageous in that they hinder convenience in clinical practice.

To date, the clinical significance of equivocal amyloid PET has not been well established due to the relative lack of long-term follow-up studies of current F-18 amyloid PET tracers, since they have only been introduced for a few years. We chose the ADNI cohort to show the clinical significance of equivocal amyloid PET because it is one of the oldest and longest cohorts to use F-18 florbetapir PET as a biomarker for Aβ.

Nevertheless, the majority of the subjects with equivocal amyloid PET were above the SUVR positive threshold, and none of the subjects converted to AD during the 4-year follow-up. These findings suggest that they are at the beginning of amyloid cascade, which is more than a decade prior to the appearance of the clinical symptoms of AD [36]. In anti-amyloid treatment of asymptomatic Alzheimer's disease (A4 study), which is the first prevention trial in clinically normal older individuals identified as "at-risk" for progression to AD on the basis of evidence of brain amyloid accumulation on PET imaging, participants must show evidence of elevated amyloid accumulation on "both" a visual read and a quantitative measurement (SUVR) of the F-18 florbetapir PET scan [37]. Therefore, subjects with equivocal amyloid PET in this study were not the best candidates for the A4 study since they were not at increased risk for cognitive decline or for developing AD by the end of the study.

There are several limitations of the current study. First, the low rate of AD conversion in subjects with equivocal amyloid PET could be due to the small number of subjects. Since subjects with equivocal amyloid PET findings were usually less than 10%, further study with a larger cohort than the ADNI is required, which is usually not achievable practically. Second, we classified equivocal amyloid PET findings as diffuse and regional patterns but could not conclude whether their fate is different with the current sample size. Third, the number of subjects with AD was too small, and as a result, we were unable to decide the clinical significance of equivocal amyloid PET in AD.

Declarations

Ethical Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board of the respective institutions and with the Helsinki declaration as revised in 2013 and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all participants.

Conflict of Interest Minyoung Oh, Minjung Seo, Sun Young Oh, Heeyoung Kim, Byung Wook Choi, Jungsu S. Oh, and Jae Seung Kim declare that they have no conflicts of interest

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