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Cerebral Amyloid Quantification in Cognitively Normal Korean Adults Using F-18 Florbetaben PET

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Abstract

Purpose To investigate regional cerebral amyloid beta retention in cognitively normal Korean adults using F-18 florbetaben (FBB).

Methods We prospectively analyzed F-18 FBB positron emission tomography (PET)/CT scans of 30 cognitively healthy adults (age range, 50–70 years) using automated quantification. The standardized uptake value ratios (SUVRs) of F-18 FBB were calculated for predefined regions by normalizing the regional count with cerebellar cortex.

Results The distribution of amyloid beta for each brain region revealed no age-related trends ($p > 0.05$). From all subjects, mean SUVR of amyloid deposit was 1.30 ± 0.18. The right parietal lobe showed the highest SUVR value (1.46 ± 0.23), whereas the right frontal lobe and left precuneus showed the lowest SUVR (1.23 ± 0.25).

Conclusions We provide reference values of normative data obtained from healthy elderly Koreans and suggest its use for accurate diagnosis of patients with Alzheimer's disease.

Keywords Alzheimer's disease · F-18 florbetaben · Healthy · SUVR

Introduction

Alzheimer's disease (AD) is the most common type of dementia that lowers quality of life for both patients and families. The extraneuronal accumulation of aggregated beta amyloid plaques is one of the pathologic hallmark of AD and known as an initial pathogenic step in AD progression. This laminar-structured protein is highly polymorphous and has neurotoxic properties. It derives from the cleavage of the normal transmembrane protein "amyloid precursor protein (APP)", and APP processing is the key factor of amyloid concentration in the brain. Amyloid eventually triggers intraneuronal accumulation of the tau protein, leading to neuronal injury. This is referred to as the amyloid cascade hypothesis [1]. Just 20 years ago, postmortem autopsy was the only way to definitively diagnose AD. It is now possible to achieve a whole-brain view of the distribution of abnormal changes, at each stage of disease progression, using imaging biomarkers in vivo. This assists in early detection and treatment of patients with suspected AD.

Moreover, amyloid positron emission tomography (PET) studies move toward quantitative analysis of amyloid accumulation, beyond traditional visual and binomial categorization of images as either "positive" or "negative." This approach is helpful to make reliable diagnosis in case of ambiguous PET scan. To capture the changes of amyloid burden precisely, familiarity with normative data is essential.

The objective of this study is to establish a database of information obtained from a cognitively normal Korean cohort following quantification of F-18 FBB PET images.

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Materials and Methods

Participants

From 2016 to 2017, we recruited patients, aged 50s through 70s, without any histories of cognitive impairment and examined them in neurology department of Dong-A University Medical Center. Participants completed detailed neuropsychological assessments, including the Seoul Neuropsychological Screening Battery (SNSB). The SNSB includes comprehensive cognitive tests for evaluating levels of cognitive functioning or impairment across five different cognitive domains: attention, language and related functions, visuospatial functions, memory, and frontal/executive functions. The estimated completion time for the whole battery is 1.5 to 2 h.

Participants with any neurological, medical, or psychiatric diseases were excluded from this study. All participants had normal neurological findings, Mini-Mental State Examination (MMSE) scores of 24 or greater, and Clinical Dementia Rating (CDR) scale scores < 0.5 with at least 6 years of education. Informed consent was obtained from all participants. The study protocol was reviewed and approved by the Institutional Review Board of our hospital.

PET Acquisition

Following completion of a comprehensive neurological exam, all participants underwent F-18 FBB PET/CT. All PET examinations were performed using a Biograph 40 mCT Flow PET/CT scanner (Siemens Healthcare, Knoxville, TN). The UltraHD-PET (TrueX-TOF) was used to reconstruct all PET images. F-18 florbetaben (NeuraCeq, Piramal Pharma) dose of 300 MBq was intravenously injected followed by saline flush. Thereafter, participants rested in a bed within a quiet room and dim lighting. PET/computed tomography (CT) acquisition commenced 90 min after radiotracer injection. Velcro straps secured the participant's head to minimize motion artifacts. Helical CT was performed with a rotation time of 0.5 s at 100 kVp and 228 mAs, without an intravenous contrast agent. PET followed immediately and was acquired for 20 min in 3-dimensional mode. All images were acquired from the skull vertex to the skull base.

Visual Assessment

All PET images were read by three qualified experts masked to clinical diagnosis and all other clinical findings. Axial images of the brain area reviewed from inferior to superior, with the cerebellum reviewed first and examined of asymmetrical atrophy. Readers were permitted to use grayscale to review axial images with operationalized assessment methods of regional cortical tracer uptake (RCTU) and brain amyloid plaque load (BAPL). The recommended cortical regions for investigation are lateral temporal lobe, frontal lobe, and posterior cingulate/precuneus and parietal lobe by the manufacturer. BAPL 1 is considered a negative scan with no tracer uptake in aforementioned areas, and both BAPL 2 (moderate tracer uptake) and 3 (definite tracer uptake) are considered a positive scan for amyloid. Negative scan normally shows nonspecific white matter uptake and little or no binding in the gray matter with clear gray-white matter contrast. Thus, normal scan shows white matter distribution not reaching into the cortical ribbon. Participants with positive amyloid scans were excluded from the study.

Image Analysis

PMOD 3.6 (PMOD Technologies, Zurich, Switzerland) was used for image quantitative analysis. The transformation matrix of each participant was obtained by fusing the CT template of the PMOD and the CT image of the participant. PET images were then spatially normalized through the transformation matrix of each participant and applied to an automated anatomical labeling template of PMOD (AAL-Merged atlas). F-18 FBB PET images were spatially normalized into MNI (Montreal Neurological Institute) spatial templates. AAL-Merged atlas was applied to spatially normalized F-18 FBB PET images (Fig. 1). Data from 71 gray-matter volume of interest (VOIs) are combined to result in the amyloid composite brain regions such as frontal cortex (11, 12, 13, 14: superior frontal gyrus, middle frontal gyrus), temporal cortex (61, 62, 65, 66: Heschl gyrus, temporal lobe), parietal cortex (45, 46, 63, 64: supramarginal gyrus, parietal lobe), posterior cingulate (25, 26: posterior cingulum), and precuneus (49, 50: precuneus). Standardized uptake value ratios (SUVRs) were calculated from each region. Global SUVR was calculated as the arithmetic mean of above 5 regions. The cerebellar cortex, which is expected to be free of amyloid deposition, was used as a reference tissue. A visual inspection was performed during the co-registration step to check the delineation of the gray matter and white matter of cerebellum as a quality control.

Statistical Analysis

Normal distributions for all continuous variables were evaluated using Kolomogorov-Smirnov test. All variables were compared between age groups using Kruskal-Wallis test or analysis of variance(ANOVA). We organized 3 subgroups by age in 10-year intervals: 50–59 years, 60–69 years, 70–79 years. Age and CDR score were compared using Kruskal-Wallis test whereas other variables were compared using ANOVA. For the result of age and education years, post hoc analysis was performed using Student-Newman-Keuls (SNK) method. Categorical variable such as sex ratio was

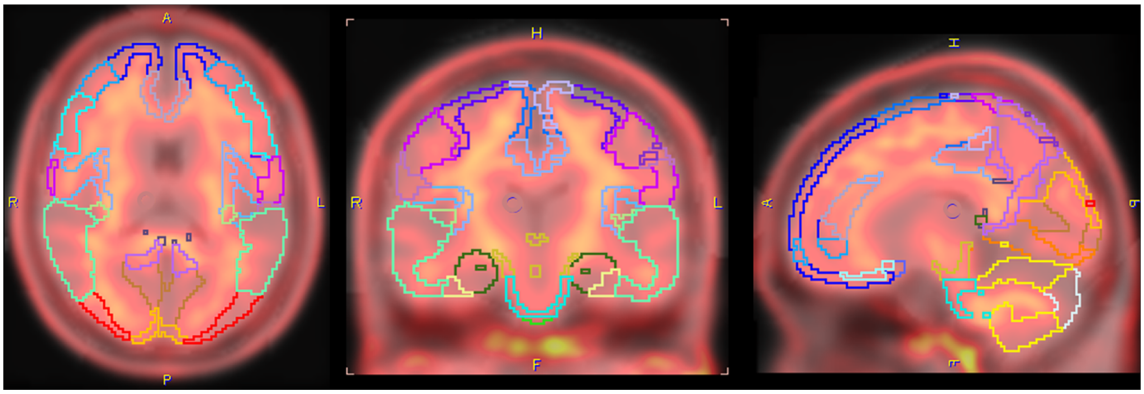

Fig. 1 Brain parcellation results overlaid on fusion images of CT and amyloid PET with intersection of VOIs with a gray and white matter probability mask

assessed using Fisher's exact test. Statistical analyses were performed using MedCalc Statistical Software version 16.4.3. All p values were 2-sided. Statistical significance was considered when p values were < 0.05.

Results

Demographics

Normal data were extracted from 30 participants with concordant visual assessments of negative scans for amyloid deposits. Demographic and cognitive scores for each group are summarized in Table 1. The gender ratio was not balanced because of the makeup of the healthy control cohort. However, there were no statistical differences in the ratios from each age group.

The mean cognitive scores were not significantly different from each other ($p > 0.05$). The total education duration values for each age group were significantly different ($p = 0.035$) and participants in their 70s demonstrated significantly fewer years of education compared with the other groups (7.80 ± 3.93).

Quantitative Analysis

The mean SUVRs of brain regions for the age group of 50–59 years, 60–69 years, and 70–79 years are summarized in Table 2. SUVR values obtained from each brain region showed no significant differences ($p > 0.05$) in the amyloid burden among the three groups (Fig. 2).

From all subjects, mean SUVR of amyloid deposit was 1.30 ± 0.18. The minimum SUVR of amyloid retention was 0.85, the maximum 1.52. And the first quartile SUVR value was 1.22, the median 1.35, and the third 1.44. The 95% confidence interval of SUVR range was 1.23–1.37.

For each brain region, the SUVR of the left frontal lobe (1.28 ± 0.25), right frontal lobe (1.23 ± 0.25), left temporal lobe (1.32 ± 0.17), right temporal lobe (1.42 ± 0.19), left parietal lobe (1.37 ± 0.15), right parietal lobe (1.46 ± 0.23), left

Table 1 Demographics of subjects included in the study

	50–59 years	60–69 years	70–79 years	Total	p value
Number of subjects	10	10	10	30	
Male	8 (80%)	9 (90%)	6 (60%)	23 (77%)	0.27
Age (years)	55.71 ± 2.45	63.82 ± 2.48	74.72 ± 2.54	65.20 ± 7.99	< 0.001*
Education (years)	11.32 ± 2.66	12.21 ± 3.93	7.80 ± 3.93	10.43 ± 3.95	0.04*
MMSE score	28.51 ± 1.08	28.23 ± 1.47	27.81 ± 1.22	28.17 ± 1.26	0.56
CDR score	0.25 ± 0.26	0.35 ± 0.24	0.35 ± 0.24	0.32 ± 0.40	0.57
Attention	72.43 ± 26.83	62.86 ± 27.88	81.7 ± 25.10	72.3 ± 26.41	0.65
Frontal/executive function	69.13 ± 4.83	62.18 ± 20.06	71.1 ± 21.07	61.4 ± 20.09	0.73
Language	55.90 ± 21.93	63.57 ± 11.21	64.8 ± 26.21	65.2 ± 20.05	0.59
Memory	58.73 ± 20.70	60.90 ± 27.21	65.7 ± 28.68	61.7 ± 24.61	0.83
Visuospatial function	68.48 ± 12.87	66.55 ± 17.67	60.8 ± 28.76	67.4 ± 25.15	0.7

*$p < 0.05$

Table 2 Quantitative PET data analysis by brain region in each age group

Region of SUVR	Mean ± SD				F-ratio	*p* value
	50–59 years	60–69 years	70–79 years	Total		
Frontal lobe (L)	1.20 ± 0.26	1.30 ± 0.31	1.34 ± 0.13	1.28 ± 0.25	1.70	0.19
Frontal lobe (R)	1.13 ± 0.26	1.27 ± 0.31	1.30 ± 0.13	1.23 ± 0.25	2.46	0.10
Temporal lobe (L)	1.28 ± 0.21	1.36 ± 0.17	1.31 ± 0.11	1.32 ± 0.17	0.56	0.58
Temporal lobe (R)	1.40 ± 0.21	1.43 ± 0.21	1.42 ± 0.16	1.42 ± 0.19	0.04	0.96
Parietal lobe (L)	1.32 ± 0.16	1.34 ± 0.19	1.45 ± 0.07	1.37 ± 0.15	2.28	0.12
Parietal lobe (R)	1.40 ± 0.31	1.47 ± 0.23	1.50 ± 0.13	1.46 ± 0.23	0.42	0.66
Posterior cingulate (L)	1.26 ± 0.18	1.31 ± 0.12	1.32 ± 0.11	1.30 ± 0.14	0.49	0.62
Posterior cingulate (R)	1.15 ± 0.26	1.25 ± 0.31	1.31 ± 0.13	1.24 ± 0.25	1.00	0.38
Precuneus (L)	1.12 ± 0.25	1.27 ± 0.32	1.28 ± 0.12	1.23 ± 0.25	1.31	0.29
Precuneus (R)	1.34 ± 0.26	1.40 ± 0.24	1.45 ± 0.11	1.40 ± 0.21	0.74	0.49
Global (composite)	1.22 ± 0.23	1.31 ± 0.19	1.36 ± 0.09	1.30 ± 0.18	1.52	0.24

L, left; *R*, right

posterior cingulate (1.30 ± 0.14), right posterior cingulate (1.24 ± 0.25), left precuneus (1.23 ± 0.25), and right precuneus (1.40 ± 0.21) is shown with the minimum value, the first quartile (Q25), the median (Q50), the third quartile (Q75), and the maximum value in Table 3.

SUVR value was greatest in the right parietal lobe (1.46 ± 0.23), whereas the right frontal lobe and left precuneus showed the lowest SUVR (1.23 ± 0.25).

Discussion

To the best of our knowledge, this was the first study of normative SUVR values for elderly Koreans using F-18 FBB scans. Neuropathological studies have repeatedly demonstrated that aggregated proteins also accumulate in the brains of healthy elderly individuals [2]. Patterns of amyloid beta accumulation by age, among healthy Koreans, have never been studied with F-18 florbetaben.

Clearance slows and white matter becomes less stable with age [3]. The impact of the spillover from adjacent white matter may be prominent in normal controls where there is very little amyloid deposition in cortical regions, and high non-specific binding in white matter. High cerebral white matter uptake has been reported for all amyloid PET tracers and is thought to be related to non-specific myelin binding [4, 5]. Owing to these findings, amyloid retention is expected to increase with age. On the other hand, we found no significant age effect for amyloid accumulation in vivo. The results suggest that amyloid deposition does not vary with increasing age in

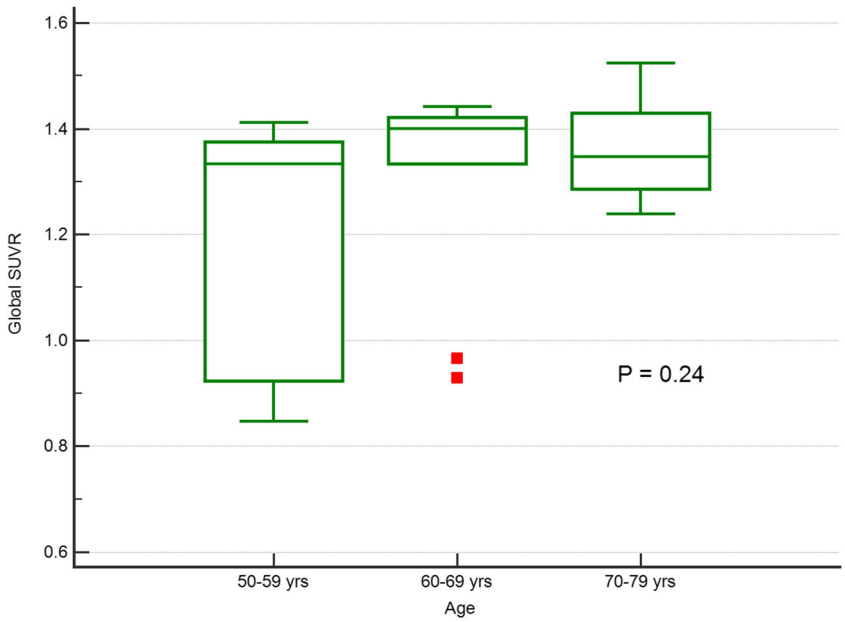

Fig. 2 Box plotting of SUVR by age subgroup. Each age group showed mean composite SUVR values in the following distribution: 50–59 years ($n = 10$), 1.22 ± 0.23; 60–69 years ($n = 10$), 1.31 ± 0.19; and 70–79 years ($n = 10$), 1.36 ± 0.09 ($p = 0.24$)

Table 3 Descriptive statistics of regional SUVRs in all subjects

Region of SUVR	Mean ± SD	Minimum	Q50 (Q25, Q75)	Maximum	95% CI
Frontal lobe (L)	1.28 ± 0.25	0.68	1.35 (1.22, 1.44)	1.61	1.22–1.34
Frontal lobe (R)	1.23 ± 0.25	0.67	1.31 (1.17, 1.40)	1.62	1.17–1.30
Temporal lobe (L)	1.32 ± 0.17	0.92	1.38 (1.24, 1.42)	1.53	1.26–1.38
Temporal lobe (R)	1.42 ± 0.19	1.02	1.46 (1.40, 1.55)	1.72	1.35–1.48
Parietal lobe (L)	1.37 ± 0.15	0.99	1.41 (1.33, 1.45)	1.60	1.32–1.43
Parietal lobe (R)	1.46 ± 0.23	0.87	1.55 (1.43, 1.59)	1.69	1.37–1.54
Posterior cingulate (L)	1.30 ± 0.14	0.89	1.34 (1.20, 1.39)	1.51	1.25–1.35
Posterior cingulate (R)	1.24 ± 0.25	0.68	1.31 (1.20, 1.40)	1.57	1.15–1.32
Precuneus (L)	1.23 ± 0.25	0.70	1.28 (1.18, 1.38)	1.58	1.14–1.32
Precuneus (R)	1.40 ± 0.21	0.91	1.48 (1.36, 1.52)	1.64	1.32–1.47
Global (composite)	1.30 ± 0.18	0.85	1.36 (1.29, 1.41)	1.52	1.23–1.37

L, left; *R*, right

cognitively normal participants. Our results agree with earlier work that showed no age-related effects in Japanese healthy control subjects, compared with Caucasian healthy control subjects [6]. A previous study found no difference in amyloid deposition between Japanese and Caucasian healthy control subjects, but age-related trend appeared only in Caucasian group [6, 7]. Thus, fibrillary amyloid retention appears to *not* increase with age among individuals of Asian descent. Of note, ethnicity affects both the prevalence and incidence of AD. Research on racial differences in AD has increased dramatically in recent years [8, 9].

SUVRs of F-18 FBB were high in the both parietal lobes compared with other brain regions. Somewhat high SUVR value in parietal lobe might be related to cortical thinning in the parietal lobes of elderly individuals. Cortical thickness was negatively correlated with brain amyloid deposition in the PiB [10].

The present study had several limitations. First, normal elderly participants were diagnosed using only clinical criteria. Genetic markers, such as APOE or MR imaging, which can help to compensate for atrophic changes using scaled values such as medial temporal atrophy (Sheltens scale), were unavailable. Second, since MR information was unavailable, CT-based spatial normalization was performed instead. Considering the fact that it is not easy to obtain MR images at the clinical setting, there was a study which compared low-dose CT-based normalization and MR-based normalization using F-18 FBB PET [11]. Fortunately, there was no significant difference in the SUVR values between the two spatial normalization methods. Third, the years of education and sex ratios were not able to be controlled. During visual analyses, positive scans were excluded on purpose. We established normative reference levels using negative scans only. This was different from a previous report that showed that 10% of healthy controls produced positive scans on F-18 FBB PET [12]. Last, since this study was performed with a relatively limited sample size in a single institution, our results may be difficult to generalize to the population as a while.

Conclusion

We examined the distribution patterns of F-18 FBB for amyloid in predefined brain regions, and documented normative data of semi-quantification for healthy Korean adults. These results could be used to select a target group requiring closure surveillance for AD, thereby facilitating early intervention during the optimal period before considerable amyloid accumulation and cognitive decline.

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Compliance with Ethical Standards

Conflict of Interest Jieun Jeong, Yong Jin Jeong, Kyung Won Park, and Do-Young Kang declare that they have no conflict of interest. This research was supported by the project at Institute of Convergence Bio-Health, DongA University, funded by Busan Institute of S&T Evaluation and Planning.

Ethical Statement This study was performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1964 and its later revisions.

Informed Consent Informed consent was obtained from all individual participants included in this prospective study.

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