Original Article

Yonsei Med J 2022 Mar;63(3):259-264
https://doi.org/10.3349/ymj.2022.63.3.259

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

^{18}F-THK5351 PET Positivity and Longitudinal Changes in Cognitive Function in β-Amyloid-Negative Amnestic Mild Cognitive Impairment

Min Young Chun[1], Jongmin Lee[2], Jee Hyang Jeong[3], Jee Hoon Roh[4,5], Seung Jun Oh[6], Minyoung Oh[6], Jungsu S. Oh[6], Jae Seung Kim[6], Seung Hwan Moon[7], Sook-young Woo[8], Young Ju Kim[1,9], Yeong Sim Choe[1,9,10,11], Hee Jin Kim[1,11,12,13], Duk L. Na[1,11,13,14], Hyemin Jang[1,13], and Sang Won Seo[1,11,12,13,15]

[1]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul;
[2]Department of Neurology, Myongji St. Mary's Hospital, Seoul;
[3]Department of Neurology, Ewha Womans University Seoul Hospital, Ewha Womans University College of Medicine, Seoul;
[4]Department of Physiology, Korea University College of Medicine, Seoul;
[5]Neuroscience Research Institute, Korea University College of Medicine, Seoul;
[6]Department of Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul;
[7]Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul;
[8]Biostatistics Team, Samsung Biomedical Research Institute, Seoul;
[9]Neuroscience Center, Samsung Medical Center, Seoul;
[10]Samsung Alzheimer Research Center, Samsung Medical Center, Seoul;
[11]Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul;
[12]Department of Digital Health, SAIHST, Sungkyunkwan University, Seoul;
[13]Alzheimer's Disease Convergence Research Center, Samsung Medical Center, Seoul;
[14]Stem Cell and Regenerative Medicine Institute, Samsung Medical Center, Seoul;
[15]Department of Intelligent Precision Healthcare Convergence, Sungkyunkwan University School of Medicine, Suwon, Korea.

Purpose: Neuroinflammation is considered an important pathway associated with several diseases that result in cognitive decline. ^{18}F-THK5351 positron emission tomography (PET) signals might indicate the presence of neuroinflammation, as well as Alzheimer's disease-type tau aggregates. β-amyloid (Aβ)-negative (Aβ−) amnestic mild cognitive impairment (aMCI) may be associated with non-Alzheimer's disease pathophysiology. Accordingly, we investigated associations between ^{18}F-THK5351 PET positivity and cognitive decline among Aβ− aMCI patients.

Materials and Methods: The present study included 25 amyloid PET negative aMCI patients who underwent a minimum of two follow-up neuropsychological evaluations, including clinical dementia rating-sum of boxes (CDR-SOB). The patients were classified into two groups: ^{18}F-THK5351-positive and -negative groups. The present study used a linear mixed effects model to estimate the effects of ^{18}F-THK5351 PET positivity on cognitive prognosis among Aβ− aMCI patients.

Results: Among the 25 Aβ− aMCI patients, 10 (40.0%) were ^{18}F-THK5351 positive. The patients in the ^{18}F-THK5351-positive group were older than those in the ^{18}F-THK5351-negative group (77.4±2.2 years vs. 70.0±5.5 years; p<0.001). There was no difference between the two groups with regard to the proportion of apolipoprotein E ε4 carriers. Interestingly, however, the CDR-SOB scores of the ^{18}F-THK5351-positive group deteriorated at a faster rate than those of the ^{18}F-THK5351-negative group (B=0.003, p=0.033).

Received: August 27, 2021 **Revised:** December 5, 2021 **Accepted:** December 7, 2021
Co-corresponding authors: Sang Won Seo, MD, PhD, Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Tel: +82-2-3410-1233, Fax: +82-2-3410-0052, E-mail: sangwonseo@empas.com and
Hyemin Jang, MD, PhD, Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Tel: +82-2-3410-1426, Fax: +82-2-3410-0052, E-mail: hmjang57@gmail.com

•The authors have no potential conflicts of interest to disclose.

Conclusion: The results of the present study suggest that increased ^{18}F-THK5351 uptake might be a useful predictor of poor prognosis among Aβ– aMCI patients, which might be associated with increased neuroinflammation (ClinicalTrials.gov NCT02656498).

Key Words: Positron emission tomography, mild cognitive impairment, amyloid, tau proteins, inflammation

INTRODUCTION

^{18}F-THK5351 is a single S-enantiomer quinoline-derivative probe that was originally developed as a tau positron emission tomography (PET) tracer, on account of its high affinity for pathologic Alzheimer's disease-type (AD-type) tau aggregates.[1-3] However, previous studies have reported that increased ^{18}F-THK5351 uptake might also be associated with increased neuroinflammation, as well as tau aggregates.[4,5] Previous studies have demonstrated that ^{18}F-THK5351 can bind to monoamine oxidase B (MAO-B),[4,5] a marker of neuroinflammation, and that the administration of selegiline, an MAO-B inhibitor, results in decreased uptake of ^{18}F-THK5351.[5] Hence, ^{18}F-THK5351 might indicate neuroinflammation induced by reactive astrocytes as well as AD-type tau aggregates.[6,7]

Amnestic mild cognitive impairment (aMCI) refers to the prodromal stage of dementia. Previously, it was considered that patients with aMCI had a high likelihood of exhibiting β-amyloid (Aβ) deposition and progression to AD dementia. However, approximately 50% of patients with aMCI appear to be Aβ negative (Aβ–) on radiographic evaluation using PET.[8-10] Previously, we demonstrated that Aβ– aMCI might be related to non-AD pathophysiology, including other neurodegenerative diseases, cerebrovascular diseases, or psychiatric diseases.[11,12] Furthermore, in a previous study, 25% of the patients with Aβ– aMCI progressed to dementia within 3 years.[11] Since neuroinflammation is considered to be an important common pathway associated with several diseases that eventually result in cognitive decline, Aβ– aMCI patients might have underlying neuroinflammation in the brain.[13,14] However, to the best of our knowledge, the effects of neuroinflammation on cognitive decline in Aβ– aMCI patients have not been meticulously investigated. Considering that increased ^{18}F-THK5351 uptake may indicate the presence of neuroinflammation in patients with Aβ– aMCI, it is reasonable to expect that a sizeable proportion of Aβ– aMCI patients will be ^{18}F-THK5351 positive, which might lead to a rapid cognitive decline in such patients.

In the present study, we investigated the proportion of ^{18}F-THK5351-positivity among Aβ– aMCI patients. We also assessed whether ^{18}F-THK5351 PET positivity might be a predictor of poor prognosis in Aβ– aMCI patients, which was determined using the clinical dementia rating-sum of boxes (CDR-SOB).

MATERIALS AND METHODS

Participants

A total of 70 participants with aMCI was prospectively enrolled in the MEMORI trials performed at Asan Medical Center (AMC) and Samsung Medical Center (SMC) from January 2016 to August 2017. The participants with aMCI met the following criteria proposed by Petersen, et al.[15]: 1) subjective memory complaints by the patient or an informant; 2) relatively normal performance in other cognitive domains; 3) normal activities of daily living, as judged clinically; 4) objective memory decline below -1.0 standard deviation (SD) on either verbal or visual memory tests; and 5) not demented.

All participants underwent ^{18}F-THK5351 PET of the brain for the detection of tau proteins, ^{18}F-florbetaben PET for the detection of Aβ, brain magnetic resonance imaging (MRI), and neuropsychological tests. Demographic and clinical data, including the apolipoprotein E (APOE) genotype, were also documented. Participants with brain tumor, stroke, traumatic brain injury, or encephalitis were excluded from the study.

The present study was approved by the Institutional Review Board for Human Research at both institutions (AMC and SMC) and written informed consent was obtained from all the participants (AMC 2016-0023; SMC 2015-09-880) and written informed consent was obtained from all the participants.

Magnetic resonance (MR) image acquisition

A 3.0-Tesla Philips Intera Achieva MR scanner (Philips Healthcare; Eindhoven, The Netherlands) was used to obtain three-dimensional, volumetric, T1-weighted MR images (images obtained at AMC: repetition time, 9.9 ms; echo time, 4.6 ms; voxel size, 1.0×1.0×0.5 mm; slice number, 360; images obtained at SMC: repetition time, 6.8 ms; echo time, 3.1 ms; voxel size, 1.11×1.11×1.2 mm; slice number, 170).[16] The present study used the resultant data to generate cortical volumes of interest for the quantification and partial volume correction of PET images.

Acquisition of ^{18}F-florbetaben and ^{18}F-THK5351 PET images

A Discovery STE PET/CT scanner (GE Healthcare; at SMC) or Discovery 690, 710, and 690 Elite PET/CT scanners (GE Healthcare; Milwaukee, WI, USA; at AMC) were used to acquire the PET images using uniform imaging/reconstruction protocols, as described previously.[7,17] The ^{18}F-THK5351 PET images were obtained with an acquisition time of 20 min, commencing 50

https://doi.org/10.3349/ymj.2022.63.3.259

min after the intravenous administration of 185±18.5 MBq of ^{18}F-THK5351; the ^{18}F-florbetaben PET images were obtained with an acquisition time of 20 min, starting 90 min after the intravenous administration of 300±30 MBq of ^{18}F-florbetaben.

^{18}F-THK5351 PET image processing

The PET image of each participant was precisely co-registered to respective T1-weighted MRI data using the SPM8 (Statistical Parametric Mapping) tool (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London) in MATLAB R2014b software for Windows (The MathWorks, Natick, MA, USA). A global region of interest (ROI) concerning the regions of the cerebral cortex was created on the basis of images of the frontal, temporal, parietal, and occipital lobes and the posterior cingulate gyri, as described previously.[18] The aforementioned regions of the cortex were segmented from individual T1-weighted MR images using SPM8 and an automated anatomical labeling template.[19] In the present study, global standardized uptake value ratio (SUVR) was calculated using weighted-mean volumes of ROIs and normalized to the mean intensity of the cerebellar gray matter using a mask image.[20]

The present study employed iterative outlier methods with global SUVR values to evaluate ^{18}F-THK5351 PET positivity. A total of 34 cognitively normal participants above the age of 59 years (range: 59–79 years) was assessed to determine the cut-off value of ^{18}F-THK5351 PET global SUVR, which was computed as 1.37. Accordingly, in this study, if the estimated SUVR value of ^{18}F-THK5351 PET exceeded 1.37, the patient was considered to be ^{18}F-THK5351 positive.

Visual assessment of ^{18}F-florbetaben PET images

The present study assessed four cortical regions, including the frontal, lateral temporal, posterior cingulate/precuneus, and parietal cortices, on grayscale ^{18}F-florbetaben PET images acquired in the axial plane.[21] A regional cortical tracer uptake system was used to assess the tracer uptake; the global uptake was evaluated with the brain amyloid plaque load scale. As the current study targeted Aβ− aMCI patients, the 33 (47.2%) ^{18}F-florbetaben-positive aMCI participants were excluded from the analysis (Fig. 1).

Neuropsychological assessments

All participants underwent the Seoul Neuropsychological Screening Battery (SNSB),[22,23] a standardized neuropsychological test battery that is widely used in South Korea and assesses five cognitive domains: attention, visuospatial function, language, memory, and executive function. A z-score on the SNSB below -1.0 SD of the reference score among patients of comparable age, sex, and education is regarded as abnormal. In addition, the current study assessed the CDR-SOB scores of the participants.

Clinical follow-up

Clinical follow-up was performed until September 2019. Among the ^{18}F-florbetaben-negative aMCI participants, data pertaining to 25 participants who completed a minimum of two follow-up neuropsychological tests were retrospectively collected (Fig. 1). The average duration of follow-up was 14.9±13.7 months, and the follow-up evaluations were performed an average of 2.06±1.01 times.

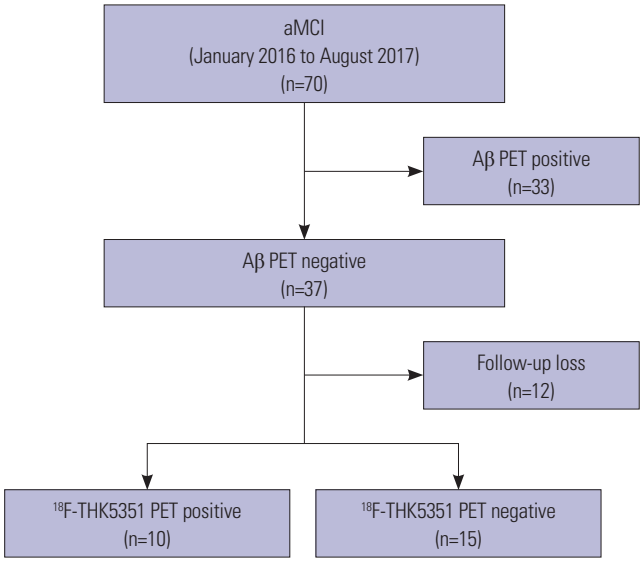

Fig. 1. Flow chart depicting the process of participant enrollment. aMCI, amnestic mild cognitive impairment; PET, positron emission tomography.

Statistics

The present study compared the demographic and clinical variables pertaining to the ^{18}F-THK5351-positive and -negative participants among the ^{18}F-florbetaben-negative aMCI patients using Student's t-test and chi-square test for continuous and categorical variables, respectively. The current study employed a linear mixed effects model to analyze the effects of ^{18}F-THK5351 positivity and negativity on longitudinal changes in CDR-SOB scores, which is represented as follows:

$$\text{longitudinal CDR-SOB changes} = \beta 0 + \beta 1 \times \text{THK positivity} + \beta 2 \times \text{time} + \beta 3 \times \text{THK positivity} \times \text{time} + 1|\text{subject} + \text{covariates},$$

where the participant was included as a random effect and baseline age, sex, education, and APOE ε4 carrier status were included as covariates.

In the present study, a two-tailed $p<0.05$ was considered statistically significant. Statistical analysis was performed using the nlme package in R 4.0.3 (Vienna, Austria; http://www.R-project.org/).

RESULTS

Demographics of the participants

The demographic and clinical characteristics of the participants

in this study are summarized in Table 1. Among the 25 ^{18}F-florbetaben-negative aMCI participants, 10 (40.0%) were ^{18}F-THK5351 positive. The mean value of ^{18}F-THK5351 SUVR was higher in the ^{18}F-THK5351-positive participants (1.457±0.083) than in the ^{18}F-THK5351-negative participants (1.290±0.093). Also, the participants in the ^{18}F-THK5351-positive group were older than those in the ^{18}F-THK5351-negative group (^{18}F-THK5351-positive 77.4±2.2 years vs. ^{18}F-THK5351-negative 70.0±5.5 years; $p<$ 0.001). The present study did not observe any difference between the ^{18}F-THK5351-positive and -negative groups with regard to the proportion of female patients (50.0% vs. 53.3%), APOE ε4 carriers (30.0% vs. 33.3%), years of education (11.6±4.2 years vs. 11.6±5.1 years), and baseline CDR-SOB (1.85±1.13 vs. 1.40±0.81) scores.

Table 1. Demographic and Clinical Characteristics of ^{18}F-Florbetaben PET-Negative aMCI Participants Obtained at Baseline

	^{18}F-THK5351 positive (n=10)	^{18}F-THK5351 negative (n=15)	*p* value
Age, yr	77.4±2.2 (73–80)	70.0±5.5 (62–78)	<0.001
Sex, female	5 (50.0)	8 (53.3)	0.870
APOE ε4 carrier	3 (30.0)	5 (33.3)	0.861
Education, yr	11.6±4.2 (6–18)	11.6±5.1 (0.5–18)	0.986
Initial CDR-SOB score	1.85±1.13 (0.5–4)	1.40±0.81 (0.5–3)	0.256
^{18}F-THK5351 PET SUVR	1.457±0.083	1.290±0.093	

PET, positron emission tomography; aMCI, amnestic mild cognitive impairment; APOE, apolipoprotein E; CDR-SOB, clinical dementia rating-sum of boxes; SUVR, standardized uptake value ratio.
Continuous variables are presented as a mean±standard deviation, and categorical variables are presented as n (%) values.

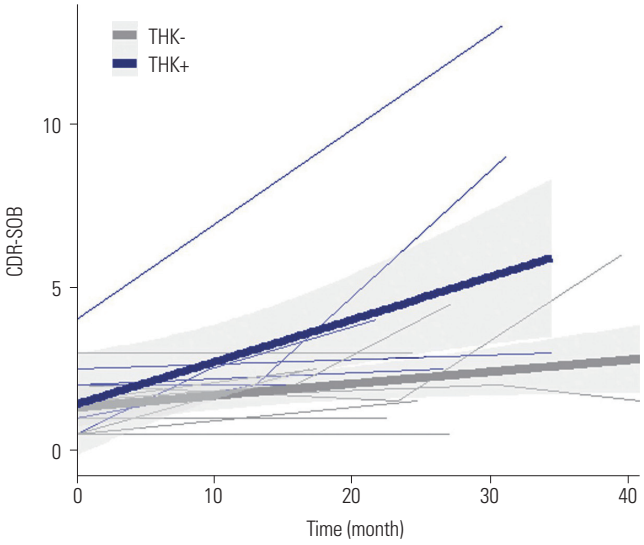

Fig. 2. Cognitive changes during the course of follow-up in the ^{18}F-THK5351-positive and -negative groups among the ^{18}F-florbetaben-negative aMCI participants. Among the ^{18}F-florbetaben-negative participants, the ^{18}F-THK5351-positive group displayed a more rapid decline in CDR-SOB scores than the ^{18}F-THK5351-negative group. aMCI, amnestic mild cognitive impairment; CDR-SOB, clinical dementia rating-sum of boxes; THK, ^{18}F-THK5351.

Comparison of longitudinal neuropsychological changes in accordance with ^{18}F-THK5351 positivity

Among the ^{18}F-florbetaben-negative aMCI participants, the longitudinal changes in CDR-SOB scores in the ^{18}F-THK5351-positive and -negative groups are shown in Fig. 2. A linear mixed effects model analysis of the CDR-SOB scores in ^{18}F-florbetaben-negative aMCI participants revealed a steeper slope in the ^{18}F-THK5351-positive individuals than ^{18}F-THK5351-negative individuals (B=0.003, p=0.033) (Fig. 2 and Table 2).

DISCUSSION

The present study reports novel data regarding the cognitive trajectory of Aβ– ^{18}F-THK5351-positive aMCI patients. The current study found that 40.0% of the Aβ– aMCI patients were ^{18}F-THK5351 positive. Moreover, Aβ– aMCI patients with ^{18}F-THK5351 positivity had a worse cognitive trajectory than Aβ- aMCI patients with ^{18}F-THK5351 negativity. Taken together, the present findings suggest that ^{18}F-THK5351 positivity might be a useful predictor of poor prognosis among Aβ– aMCI patients, which might be associated with increased neuroinflammation.

The first major finding of this study is that 40.0% of patients with amyloid PET negative aMCI display ^{18}F-THK5351 positivity. Because a precise cut-off value to evaluate ^{18}F-THK5351 positivity is lacking in existing literature, we created a cut-off value for ^{18}F-THK5351 positivity using the iterative outlier that is widely used. Previous studies that used other radiotracers for imaging tau aggregation have observed decreased tracer uptake in Aβ– aMCI patients, compared to Aβ+ aMCI patients.[24,25] However, the proportion of ^{18}F-THK5351-positive patients among the Aβ– aMCI cohort in the present study was higher than expected. The present findings might be related to neuroinflammation in the brain, as Aβ– aMCI might be associated with non-AD pathophysiology. In fact, a previous imaging–pathological correlation study by the authors that involved a patient with Creutzfeldt–Jakob disease showed that increased ^{18}F-THK5351 uptake is related to reactive astrocytes with increased MAO-B activity, but not neurofibrillary tangles.[26] Furthermore, a previous study reported that patients with neuropathologically confirmed progressive supranuclear palsy had high SUVR in an-

Table 2. Results of the Linear Mixed Effect Model for CDR-SOB Scores

	THK effect		Time effect		THK×Time	
	B (SE) (95% CI)	*p* value	B (SE) (95% CI)	*p* value	B (SE) (95% CI)	*p* value
CDR-SOB	0.384 (0.985) (-1.670–2.438)	0.701	0.002 (0.0007) (0.0006–0.004)	0.009	0.003 (0.001) (0.0003–0.005)	0.033

B, beta coefficient; CDR-SOB, clinical dementia rating-sum of boxes; THK, ^{18}F-THK5351; SE, standard error; CI, confidence interval.

https://doi.org/10.3349/ymj.2022.63.3.259

temortem ^{18}F-THK5351 PET scans, which was correlated with MAO-B levels.[27] In addition, a longitudinal study of corticobasal syndrome, which has reactive astrogliosis, showed that ^{18}F-THK5351 high uptake can be useful for monitoring the progression of astrogliosis in CBS.[28] Thus, ^{18}F-THK5351 positivity can reflect reactive astrocytosis and neuroinflammation in several neurodegeneration disorders, including Aβ− aMCI.

The second major finding in the current study is that the ^{18}F-THK5351-positive group exhibited a faster decline in the CDR-SOB scores than the ^{18}F-THK5351-negative group. Since CDR-SOB is widely accepted as a reliable measure for the assessment of the six domains of cognitive and functional performance, CDR-SOB scores are important in the assessment of severity of aMCI.[29] Furthermore, a previous study by the authors revealed that brain regions with increased ^{18}F-THK5351 uptake in Aβ− frontotemporal dementia are consistent with those in brain atrophy on MRI scans.[7] The relationship between increased ^{18}F-THK5351 uptake and cognitive decline or brain atrophy might be explained by increased neuroinflammation.[6] Indeed, research has shown that alterations in the functions of astrocytes and microglia could induce the production and secretion of inflammatory cytokines, such as interleukin-6 (IL-6), which might eventually cause neuronal injury.[13,30] Furthermore, neuroinflammation caused by oxidative damage and mitochondrial dysfunction could contribute to cognitive decline in all types of neurodegenerative dementia, as well as AD.[14]

The strength of the current study is that longitudinal follow-up neuropsychological evaluations were performed to determine the significance of ^{18}F-THK5351 PET positivity on the cognitive prognosis of Aβ− aMCI patients. However, the present study has several limitations. First, the sample size was relatively small. Second, the age difference between the ^{18}F-THK5351-positive and -negative groups may have affected the cognitive trajectories. Third, other factors related to inflammation, such as serum C-reactive protein, erythrocyte sedimentation rate, and IL-6, as well as the results pertaining to cerebrospinal fluid glial markers (e.g., chitotriosidase 1, chitinase-3-like protein 1, and glial fibrillary acidic protein) were not included for analysis.[31] Moreover, since increased ^{18}F-THK5351 uptakes in Aβ− participants might reflect other pathobiology, rather than neuroinflammation, further studies with neuroinflammation PET may be needed. Fourth, the present study involves limited pathological data to validate the findings. Fifth, the present study did not consider other pathological conditions that could contribute to cognitive impairment, including TAR DNA-binding protein, hippocampal sclerosis, argyrophilic grain disease, and Lewy body pathologies. There was no ^{18}F-THK5351 uptake pattern suggesting non-AD pathology. Finally, we decided Aβ negativity using visual assessment, which may raise the possibility that discernment of Aβ negativity was inaccurate. However, this might be mitigated to some extent in that visual assessment by experienced doctors has shown high agreement with SUVR cut-off optimization method.[32] Regardless of the abovementioned limitations, the current study is noteworthy as this is the first study to demonstrate that increased ^{18}F-THK5351 uptake can predict cognitive decline among Aβ− aMCI patients.

In conclusion, increased ^{18}F-THK5351 uptake might be a useful predictor of poor prognosis among Aβ− aMCI patients, which might be related to increased neuroinflammation in the brain.

ACKNOWLEDGEMENTS

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare and Ministry of science and ICT, Republic of Korea (grant number: HU20C0111); a National Research Council of Science & Technology (NST) grant by the Korea government (MSIP) (No. CRC-15-04-KIST); and funding (2021-ER1006-00) from the Research of Korea Disease Control and Prevention Agency.

AUTHOR CONTRIBUTIONS

Conceptualization: Min Young Chun and Jongmin Lee. Data curation: Seung Jun Oh, Minyoung Oh, Jungsu S. Oh, and Yeong Sim Choe. Formal Analysis: Sook-young Woo and Young Ju Kim. Funding acquisition: Sang Won Seo. Investigation: Jongmin Lee. Methodology: Jae Seung Kim and Seung Hwan Moon. Project administration: Jongmin Lee. Resources: Sang Won Seo. Software: Yeong Sim Choe. Supervision: Hee Jin Kim, Hyemin Jang, and Sang Won Seo. Validation: Jee Hoon Roh, Jee Hyang Jeong, and Duk L. Na. Visualization: Young Ju Kim. Writing—original draft: Min Young Chun and Yeong Sim Choe. Writing—review & editing: Hyemin Jang and Sang Won Seo. Approval of final manuscript: all authors.

ORCID iDs

Min Young Chun https://orcid.org/0000-0003-3731-6132
Jongmin Lee https://orcid.org/0000-0002-0892-6217
Jee Hyang Jeong https://orcid.org/0000-0001-7945-6956
Jee Hoon Roh https://orcid.org/0000-0002-3243-0529
Seung Jun Oh https://orcid.org/0000-0002-3769-067X
Minyoung Oh https://orcid.org/0000-0002-6840-3215
Jungsu S. Oh https://orcid.org/0000-0002-1925-8103
Jae Seung Kim https://orcid.org/0000-0003-1710-1185
Seung Hwan Moon https://orcid.org/0000-0003-4302-1920
Sook-young Woo https://orcid.org/0000-0001-6577-3221
Young Ju Kim https://orcid.org/0000-0003-2927-6724
Yeong Sim Choe https://orcid.org/0000-0001-8921-749X
Hee Jin Kim https://orcid.org/0000-0002-3186-9441
Duk L. Na https://orcid.org/0000-0002-0098-7592
Hyemin Jang https://orcid.org/0000-0003-3152-1274
Sang Won Seo https://orcid.org/0000-0002-8747-0122

REFERENCES

1. Alonso AC, Grundke-Iqbal I, Iqbal K. Alzheimer's disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules. Nat Med 1996;2:783-7.
2. Harada R, Okamura N, Furumoto S, Furukawa K, Ishiki A, Tomita N, et al. 18F-THK5351: a novel PET radiotracer for imaging neuro-

fibrillary pathology in Alzheimer disease. J Nucl Med 2016;57:208-14.
3. Lockhart SN, Baker SL, Okamura N, Furukawa K, Ishiki A, Furumoto S, et al. Dynamic PET measures of tau accumulation in cognitively normal older adults and Alzheimer's disease patients measured using [18F] THK-5351. PLoS One 2016;11:e0158460.
4. Lee MK, Hwang BY, Lee SA, Oh GJ, Choi WH, Hong SS, et al. 1-methyl-2-undecyl-4(1H)-quinolone as an irreversible and selective inhibitor of type B monoamine oxidase. Chem Pharm Bull (Tokyo) 2003;51:409-11.
5. Ng KP, Pascoal TA, Mathotaarachchi S, Therriault J, Kang MS, Shin M, et al. Monoamine oxidase B inhibitor, selegiline, reduces 18F-THK5351 uptake in the human brain. Alzheimers Res Ther 2017;9:25.
6. Harada R, Ishiki A, Kai H, Sato N, Furukawa K, Furumoto S, et al. Correlations of 18F-THK5351 PET with postmortem burden of tau and astrogliosis in Alzheimer disease. J Nucl Med 2018;59:671-4.
7. Jang YK, Lyoo CH, Park S, Oh SJ, Cho H, Oh M, et al. Head to head comparison of [18F] AV-1451 and [18F] THK5351 for tau imaging in Alzheimer's disease and frontotemporal dementia. Eur J Nucl Med Mol Imaging 2018;45:432-42.
8. Jang H, Park J, Woo S, Kim S, Kim HJ, Na DL, et al. Prediction of fast decline in amyloid positive mild cognitive impairment patients using multimodal biomarkers. Neuroimage Clin 2019;24:101941.
9. Kim SE, Woo S, Kim SW, Chin J, Kim HJ, Lee BI, et al. A nomogram for predicting amyloid PET positivity in amnestic mild cognitive impairment. J Alzheimers Dis 2018;66:681-91.
10. Ezzati A, Harvey DJ, Habeck C, Golzar A, Qureshi IA, Zammit AR, et al. Predicting amyloid-β levels in amnestic mild cognitive impairment using machine learning techniques. J Alzheimers Dis 2020;73:1211-9.
11. Ye BS, Kim HJ, Kim YJ, Jung NY, Lee JS, Lee J, et al. Longitudinal outcomes of amyloid positive versus negative amnestic mild cognitive impairments: a three-year longitudinal study. Sci Rep 2018;8:5557.
12. Ye BS, Seo SW, Kim CH, Jeon S, Kim GH, Noh Y, et al. Hippocampal and cortical atrophy in amyloid-negative mild cognitive impairments: comparison with amyloid-positive mild cognitive impairment. Neurobiol Aging 2014;35:291-300.
13. Stefaniak J, O'Brien J. Imaging of neuroinflammation in dementia: a review. J Neurol Neurosurg Psychiatry 2016;87:21-8.
14. Pasqualetti G, Brooks DJ, Edison P. The role of neuroinflammation in dementias. Curr Neurol Neurosci Rep 2015;15:17.
15. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303-8.
16. Son HJ, Oh JS, Roh JH, Seo SW, Oh M, Lee SJ, et al. Differences in gray and white matter 18F-THK5351 uptake between behavioral-variant frontotemporal dementia and other dementias. Eur J Nucl Med Mol Imaging 2019;46:357-66.
17. Park JE, Yun J, Kim SJ, Shim WH, Oh JS, Oh M, et al. Intra-individual correlations between quantitative THK-5351 PET and MRI-derived cortical volume in Alzheimer's disease differ according to disease severity and amyloid positivity. PLoS One 2019;14:e0226265.
18. Cho SH, Choe YS, Kim YJ, Kim HJ, Jang H, Kim Y, et al. Head-to-head comparison of 18F-florbetaben and 18F-flutemetamol in the cortical and striatal regions. J Alzheimers Dis 2020;76:281-90.
19. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002;15:273-89.
20. Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous MD Sr, Jagust WJ, et al. The centiloid project: standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement 2015;11:1-15.e1-4.
21. Barthel H, Gertz HJ, Dresel S, Peters O, Bartenstein P, Buerger K, et al. Cerebral amyloid-β PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. Lancet Neurol 2011;10:424-35.
22. Kang Y, Na DL, Hahn S. Seoul neuropsychological screening battery. Incheon: Human Brain Research & Consulting Co; 2003.
23. Kang SH, Park YH, Lee D, Kim JP, Chin J, Ahn Y, et al. The cortical neuroanatomy related to specific neuropsychological deficits in Alzheimer's continuum. Dement Neurocogn Disord 2019;18:77-95.
24. Ossenkoppele R, Leuzy A, Cho H, Sudre CH, Strandberg O, Smith R, et al. The impact of demographic, clinical, genetic, and imaging variables on tau PET status. Eur J Nucl Med Mol Imaging 2021;48:2245-58.
25. Smith R, Strandberg O, Mattsson-Carlgren N, Leuzy A, Palmqvist S, Pontecorvo MJ, et al. The accumulation rate of tau aggregates is higher in females and younger amyloid-positive subjects. Brain 2020;143:3805-15.
26. Kim HJ, Cho H, Park S, Jang H, Ryu YH, Choi JY, et al. THK5351 and flortaucipir PET with pathological correlation in a Creutzfeldt-Jakob disease patient: a case report. BMC Neurol 2019;19:211.
27. Ishiki A, Harada R, Kai H, Sato N, Totsune T, Tomita N, et al. Neuroimaging-pathological correlations of [18F]THK5351 PET in progressive supranuclear palsy. Acta Neuropathol Commun 2018;6:53.
28. Ezura M, Kikuchi A, Ishiki A, Okamura N, Hasegawa T, Harada R, et al. Longitudinal changes in 18F-THK5351 positron emission tomography in corticobasal syndrome. Eur J Neurol 2019;26:1205-11.
29. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 1997;9:173-6.
30. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. Science 2016;353:777-83.
31. Abu-Rumeileh S, Steinacker P, Polischi B, Mammana A, Bartoletti-Stella A, Oeckl P, et al. CSF biomarkers of neuroinflammation in distinct forms and subtypes of neurodegenerative dementia. Alzheimers Res Ther 2020;12:2.
32. Cho SH, Choe YS, Kim YJ, Lee B, Kim HJ, Jang H, et al. Concordance in detecting amyloid positivity between 18F-florbetaben and 18F-flutemetamol amyloid PET using quantitative and qualitative assessments. Sci Rep 2020;10:19576.

https://doi.org/10.3349/ymj.2022.63.3.259