LETTER TO THE EDITORS

18F-THK5351 PET for visualizing predominant lesions of pathologically confirmed corticobasal degeneration presenting with frontal behavioral-spatial syndrome

Yuji Saitoh1,2, Etsuko Imabayashi3,4, Masashi Mizutani5, Tadashi Tsukamoto1,2, Masato Hasegawa6, Yuko Saito5,7, Hiroshi Matsuda3,8, Yuji Takahashi1

Received: 19 March 2022 / Revised: 31 March 2022 / Accepted: 1 April 2022 / Published online: 13 April 2022 © The Author(s) 2022

Clinical phenotypes of corticobasal degeneration (CBD) vary and are typically presented with four phenotypes: corticobasal syndrome (CBS), frontal behavioral-spatial syndrome (FBS), nonfluent/agrammatic variant of primary progressive aphasia, and progressive supranuclear palsy syndrome [1]. FBS is the third most common phenotype of pathologically verified CBD, accounting for approximately 14% of CBD patients [1]. Conversely, the pathological features of the clinical phenotype of behavior variant frontotemporal dementia (bvFTD) also vary, and approximately 9% of these patients have been verified pathologically CBD [2]. Here, we present an autopsy-confirmed case of CBD presenting with FBS who underwent positron emission tomography (PET) with 18F-THK5351, visualizing the predominant lesion of the frontal lobes associated with the clinical phenotype.

A 72-year-old right-handed male developed gait slowing. Three years later, he lost his way when climbing mountains and was found lying. Two months later, he lost his way again in the neighborhood, and eventually, his wife started accompanying him when he went outside. He developed urinary incontinence, masked face, decreased

Dear Sirs,

*Yuji Saitoh
saito@ncnp.go.jp

1 Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8551, Japan
2 Research Center for Neurocognitive Disorders, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8551, Japan
3 Integrative Brain Imaging Center, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8551, Japan
4 Department of Molecular Imaging and Theranostics, Quantum Life and Medical Science Directorate, National Institute for Quantum Science and Technology, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan
5 Department of Laboratory Medicine, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8551, Japan
6 Dementia Research Project, Tokyo Metropolitan Institute of Medical Science, 2-1-6 Kamikitazawa, Setagaya-ku, Tokyo 156-8506, Japan
7 Present Address: Department of Neuropathology (Brain Bank for Aging Research), Tokyo Metropolitan Institute of Gerontology, 35-2 Sakaecho, Itabashi-ku, Tokyo 173-0015, Japan
8 Present Address: Department of Biofunctional Imaging, Fukushima Medical University, 2-2-1 Otemachi, Chiyoda-ku, Tokyo 100-0004, Japan

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| bvFTD        | Behavior variant frontotemporal dementia |
| 11C-PiB      | 11C-Pittsburgh compound B |
| CBD          | Corticobasal degeneration |
| DaT          | Dopamine transporter |
| 18F-FDG      | 18F-fluorodeoxyglucose |
| FBS          | Frontal behavioral-spatial syndrome |
| 123I-FP-CIT  | 123I-N-ω-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)nortropane |
| MAO-B        | Monoamine oxidase-B |
| MRI          | Magnetic resonance imaging |
| PET          | Positron emission tomography |
| PSP          | Progressive supranuclear palsy |
| SBR          | Specific binding ratio |
| SPECT        | Single-photon emission computed tomography |
| SUV          | Standardized uptake value |
speech output, visual hallucination, and abnormal behaviors, such as nocturnal wandering, pica, and apraxia. His condition was evaluated at an outpatient neurology clinic, and neurological examination revealed his masked face, bradykinesia, and rigidity of his neck and left-sided upper limb. He showed no therapeutic response to levodopa for parkinsonism. His abnormal behavior increased with time and he showed stereotyped behavior, such as keeping cleaning a room or washing his body. He visited our hospital for further evaluation of his neuropsychiatric symptoms at the age of 75.

Neurological examination revealed left-sided predominant parkinsonism, apraxia, and perseveration. He showed severe cognitive impairment and scored 19/30 on the Mini-Mental State Examination and 3/18 on the Frontal Assessment Battery. Brain magnetic resonance imaging (MRI) at the age of 75 revealed right-sided and frontal lobe dominant atrophy (Fig. 1A,B), which was verified.
using the voxel-based specific regional analysis system for Alzheimer’s disease [3] (Fig. 1C). Dopamine transporter single-photon emission computed tomography with 123I-N-ω-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)nortropane obtained 4 months before he visited us showed diffusely reduced uptake in the bilateral striata with right-sided predominance (Fig. 1D). He underwent 18F-THK5351 PET (Fig. 1E–G), 18F-fluorodeoxyglucose (18F-FDG) PET (Fig. 1H), and 11C-Pittsburgh compound B (11C-PiB) PET at the age of 75. The Z score map of 18F-THK5351 was superimposed on spatially normalized T1-weighted image (Fig. 1G). The Z scores were calculated as: (mean voxel value of 30 cognitively unimpaired subjects—patient voxel value)/standard deviation of 30 cognitively unimpaired subjects with cerebellar cortex as reference. 18F-THK5351 accumulated in the frontal lobes with right-sided predominance, as well as in the parietal lobes (Fig. 1E–G). Hypometabolism of both the frontal and parietal lobes with right-sided predominance was detected by 18F-FDG PET (Fig. 1H). Amyloid deposition was not identified by 11C-PiB PET (data not shown). He was clinically diagnosed with bvFTD underlying tauopathy, that is, frontotemporal lobar degeneration tau, according to the prominent frontal symptoms with spatial impairment, Parkinsonism, and neuroimaging findings including 18F-THK5351 PET. He died of aspiration pneumonia at the age of 76.

An autopsy was performed after consent was obtained from his family. The brain weighed 1402 g and showed cerebral atrophy, especially of the frontal and temporal lobes (Fig. 1I). There was dilation of the Sylvian fissure and mild atrophy of the frontal operculum with right-sided predominance (Fig. 1J). Microscopic assessment showed neuronal loss and an increased number of astrocytes in the cerebral cortex, especially in the frontal lobes, accompanied by abnormal rarefaction of tissue (Fig. 1K, L). Immunohistochemistry of the frontal lobes using AT8 antibody revealed phosphorylated tau-positive astrocytic plaques, pretangles, coiled bodies, and threads (Fig. 1M–O), which were presented as right-sided predominance (Fig. 1P, Q). Staining for RD4 or RD3 revealed phosphorylated 4-repeat but not 3-repeat tau-positivity (Fig. 1R, S). These tau-related pathological characteristics in the cortex were prominent in the anterior part of the frontal lobes with right-sided predominance. These were also found in the substantia nigra, subthalamic nucleus, thalamus, globus pallidus, putamen, nucleus basalis of Meynert, locus coeruleus, and inferior olivary nucleus. Western blot analysis of sarkosyl-insoluble tau from the brain showed a major doublet of 68 and 64 kDa, which corresponds to hyperphosphorylated full-length 4-repeat tau isoforms. Note the prominent C-terminal fragments of tau with ~37 kDa of this case are similar to those of CBD, but not to PSP. Bars, 5 cm (I, J), 100 µm (K–M, R, S), 50 µm (N, O), 1 mm (P, Q).

CBD corticobasal degeneration, 123I-FP-CIT 123I-N‐ω-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)nortropane, PET positron emission tomography, PSP progressive supranuclear palsy, SBR specific binding ratio, SPECT single-photon emission computed tomography, SUV standardized uptake value

using the voxel-based specific regional analysis system for Alzheimer’s disease [3] (Fig. 1C). Dopamine transporter single-photon emission computed tomography with 123I-N-ω-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)nortropane obtained 4 months before he visited us showed diffusely reduced uptake in the bilateral striata with right-sided predominance (Fig. 1D). He underwent 18F-THK5351 PET (Fig. 1E–G), 18F-fluorodeoxyglucose (18F-FDG) PET (Fig. 1H), and 11C-Pittsburgh compound B (11C-PiB) PET at the age of 75. The Z score map of 18F-THK5351 was superimposed on spatially normalized T1-weighted image (Fig. 1G). The Z scores were calculated as: (mean voxel value of 30 cognitively unimpaired subjects—patient voxel value)/standard deviation of 30 cognitively unimpaired subjects with cerebellar cortex as reference. 18F-THK5351 accumulated in the frontal lobes with right-sided predominance, as well as in the parietal lobes (Fig. 1E–G). Hypometabolism of both the frontal and parietal lobes with right-sided predominance was detected by 18F-FDG PET (Fig. 1H). Amyloid deposition was not identified by 11C-PiB PET (data not shown). He was clinically diagnosed with bvFTD underlying tauopathy, that is, frontotemporal lobar degeneration tau, according to the prominent frontal symptoms with spatial impairment, Parkinsonism, and neuroimaging findings including 18F-THK5351 PET. He died of aspiration pneumonia at the age of 76.

An autopsy was performed after consent was obtained from his family. The brain weighed 1402 g and showed cerebral atrophy, especially of the frontal and temporal lobes (Fig. 1I). There was dilation of the Sylvian fissure and mild atrophy of the frontal operculum with right-sided predominance (Fig. 1J). Microscopic assessment showed neuronal loss and an increased number of astrocytes in the cerebral cortex, especially in the frontal lobes, accompanied by abnormal rarefaction of tissue (Fig. 1K, L). Immunohistochemistry of the frontal lobes using AT8 antibody revealed phosphorylated tau-positive astrocytic plaques, pretangles, coiled bodies, and threads (Fig. 1M–O), which were presented as right-sided predominance (Fig. 1P, Q). Staining for RD4 or RD3 revealed phosphorylated 4-repeat but not 3-repeat tau-positivity (Fig. 1R, S). These tau-related pathological characteristics in the cortex were prominent in the anterior part of the frontal lobes with right-sided predominance. These were also found in the substantia nigra, subthalamic nucleus, thalamus, globus pallidus, putamen, nucleus basalis of Meynert, locus coeruleus, and inferior olivary nucleus. Western blot analysis of sarkosyl-insoluble tau from the brain showed a major doublet of 68 and 64 kDa with predominant ~37 kDa of this case are similar to those of CBD, but not to PSP. Bars, 5 cm (I, J), 100 µm (K–M, R, S), 50 µm (N, O), 1 mm (P, Q). CBD corticobasal degeneration, 123I-FP-CIT 123I-N-ω-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)nortropane, PET positron emission tomography, PSP progressive supranuclear palsy, SBR specific binding ratio, SPECT single-photon emission computed tomography, SUV standardized uptake value
these abnormalities obtained from in vivo imaging studies were verified through pathological evaluation of tau-positive deposition and astrogliosis in the frontal lobes with right-sided predominance. Despite the neuropathological features of bvFTD being heterogeneous [2], previous studies on 18F-THK5351 PET with bvFTD patients lack pathological confirmation. To our knowledge, this is the first clinicopathological case report demonstrating 18F-THK5351 accumulation in the frontal lobes in a CBD-FBS patient, in which the presence of tau-related neurodegenerative change was pathologically verified. However, our study was unable to distinguish the 18F-THK5351 accumulation derived from tau accumulation, an increased number of MAO-B positive astrocytes, or both, because of the limited discriminability of 18F-THK5351 between tau and MAO-B. Thus, pathologically, radiologically, and biochemically validated MAO-B PET tracers, which can more sensitively visualize neurodegeneration consisting of astrogliosis, are required [10]. Our findings provide the use of 18F-THK5351 PET as a marker closely associated with tau-related neurodegeneration.

In conclusion, the 18F-THK5351 PET image visualizes abnormally tau-related neurodegeneration reflecting clinicopathological severities in CBD-FBS. Our case highlights that 18F-THK5351 PET can be a potent technique for visualizing the tau-related predominant lesions of CBD-FBS and for discriminating the underlying pathologies of bvFTD.

Acknowledgements We would like to thank the patient’s family for their comments and for permitting the autopsy. We also thank all of the medical professionals engaged in the patient’s care and for technical assistance with the autopsy and pathological study. We thank Dr. Nobuyuki Okamura (Tohoku Medical and Pharmaceutical University, Tohoku University), Shozo Furumoto (Tohoku University), and Yukitsuka Kudo (Tohoku University) for providing the precursor and the reference materials for the synthesis of the tracer 18F-THK5351. We thank U-English Corporation (https://www.u-english.co.jp/) for English editing of a draft of this manuscript.

Author contributions Conception and design of the study: YS; Primary patient care and analysis of data: YS, EI, MM, TT, MH, YS, HM, YT; Drafting a significant portion of the manuscript or figures/tables: YS; Reviewing and approving the final manuscript: YS, EI, MM, TT, MH, YS, HM, YT.

Funding This study was partially supported by the Intramural Research Grant for Neurological and Psychiatric Disorders of the National Center of Neurology and Psychiatry under grant number 30-3 (to Y Saito), 30-8 (to Y Saito), and 3-3 (to Y Saito), by JSPS KAKENHI under Grant JP221S00003 (to Y Saito), JP15K09369 (to EI), and JP15K09981 (to HM), by the grants-in-aid from the Research Committee of CNS Degenerative Diseases, Research on Policy Planning and Evaluation for Rare and Intractable Diseases, Health, Labor and Welfare Sciences Research Grants, the Ministry of Health, Labor and Welfare, Japan, MEXT/JSPS KAKENHI Grant JP16H06277 (to Y Saito), and by AMED under grant JP18dm0107103 (to Y Saito).

Declarations

Conflicts of interest The authors have no competing interests to declare that are relevant to the content of this article.

Ethical approval The PET study was approved by the Institutional Review Committee of the National Center of Neurology and Psychiatry. Written informed consent was obtained from the patient or the patient’s next-of-kin for inclusion in this PET study, donation for diagnostic and research purposes, and publication as a medical report.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, Boxer AL, Dickson DW, Grossman M, Hallett M, Josephs KA, Kertesz A, Lee SE, Miller BL, Reich SG, Riley DE, Tolosa E, Troster AL, Vidalhnet M, Weiner WJ (2013) Criteria for the diagnosis of corticobasal degeneration. Neurology 80:496–503. https://doi.org/10.1212/WNL.0b013e31827f0fd1

2. Perry DC, Brown JA, Possin KL, Datta S, Trujillo A, Radke A, Karydas A, Kornak J, Sias AC, Rabinovici GD, Gorno-Tempini ML, Boxer AL, De May M, Rankin KP, Sturm VE, Lee SE, Matthews BR, Kao AW, Vossel KA, Tartaglia MC, Miller ZA, Seo SW, Sidhu M, Gaus SE, Nana AL, Vergas JNS, Hwang JL, Ossenkoppele R, Brown AB, Huang EJ, Coppola G, Rosen HJ, Geschwind D, Trojanowski JQ, Grinberg LT, Kramer JH, Miller BL, Seeley WW (2017) Clinicopathological correlations in behavioural variant frontotemporal dementia. Brain 140:3329–3345. https://doi.org/10.1093/brain/awx254

3. Matsuda H, Mizumura S, Nemoto K, Yamashita F, Imabayashi E, Sato N, Asada T (2012) Automatic voxel-based morphometry of structural MRI by SPM8 plus diffeomorphic anatomic registration through exponentiated lie algebra improves the diagnosis of probable Alzheimer Disease. AJNR Am J Neuroradiol 33:1109–1114. https://doi.org/10.3174/ajnr.A2935

4. Araï T, Ikeda K, Akiyama H, Nonaka T, Hasegawa M, Ishiguro K, Iritani S, Tsuchiya K, Iseki E, Yagishita S, Oda T, Mochizuki A (2004) Identification of amino-terminally cleaved tau fragments that distinguish progressive supranuclear palsy from corticobasal degeneration. Ann Neurol 55:72–79. https://doi.org/10.1002/ana.10793

5. Harada R, Okamura N, Furumoto S, Furukawa K, Ishiki A, Tomita N, Tago T, Hiraoka K, Wataniuki S, Shidahara M, Miyake M, Ishikawa Y, Matsuda R, Inami A, Yoshikawa T, Funaki Y, Iwata R, Tashiro M, Yanai K, Araï H, Kudo Y (2016) 18F-THK5351: a novel PET radiotracer for imaging neurofibrillary pathology in Alzheimer Disease. J Nucl Med 57:208–214. https://doi.org/10.2967/jnumed.115.164848
6. Ishiki A, Harada R, Kai H, Sato N, Totsune T, Tomita N, Watanuki S, Hiraoka K, Ishikawa Y, Funaki Y, Iwata R, Furumoto S, Tashiro M, Sasano H, Kitamoto T, Kudo Y, Yanai K, Furukawa K, Okamura N, Arai H (2018) Neuroimaging-pathological correlations of [(18)F]THK5351 PET in progressive supranuclear palsy. Acta Neuropathol Commun 6:53. https://doi.org/10.1186/s40478-018-0556-7

7. Ng KP, Pascoal TA, Mathotaarachchi S, Therriault J, Kang MS, Shin M, Guiot MC, Guo Q, Harada R, Comley RA, Massarweh G, Soucy JP, Okamura N, Gauthier S, Rosa-Neto P (2017) Monoamine oxidase B inhibitor, selegiline, reduces (18)F-THK5351 uptake in the human brain. Alzheimers Res Ther 9:25. https://doi.org/10.1186/s13195-017-0253-y

8. Saitoh Y, Imabayashi E, Mukai T, Matsuda H, Takahashi Y (2021) Visualization of motor cortex involvement by 18F-THK5351 PET potentially strengthens diagnosis of amyotrophic lateral sclerosis. Clin Nucl Med 46:243–245. https://doi.org/10.1097/Rlu.0000000000004356

9. Son HJ, Oh JS, Roh JH, Seo SW, Oh M, Lee SJ, Oh SJ, Kim JS (2019) Differences in gray and white matter (18)F-THK5351 uptake between behavioral-variant frontotemporal dementia and other dementias. Eur J Nucl Med Mol Imaging 46:357–366. https://doi.org/10.1007/s00259-018-4125-x

10. Harada R, Hayakawa Y, Ezura M, Lerdspirak P, Du Y, Ishikawa Y, Iwata R, Shidahara M, Ishiki A, Kikuchi A, Arai H, Kudo Y, Yanai K, Furumoto S, Okamura N (2021) (18)F-SMBT-1: a selective and reversible PET tracer for monoamine oxidase-B imaging. J Nucl Med 62:253–258. https://doi.org/10.2967/jnumed.120.244400