CASE

In Vivo Imaging and Autoradiography in a Case of Autopsy-Confirmed Pick Disease

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A 48-year-old, right-handed woman presented with a 2.5-year history of difficulties forming and finding words. At evaluation, she had a moderate phonetic-predominant apraxia of speech (AOS)[1] and mild agrammatic aphasia. She developed increasing impulsivity, distractibility, and inappropriate behaviors, but AOS remained the predominant clinical feature. She met the criteria for progressive AOS and behavioral variant frontotemporal dementia. At 5.5 years postonset, she was mute, yet her motor function was largely preserved. Autopsy examination, 7 years postonset, revealed Pick disease (PiD) pathology.

PRACTICAL IMPLICATIONS

In this case, the distribution of flortaucipir (FTP) PET uptake reflects the clinical manifestation and neuroanatomical distribution of Pick disease (PiD) pathology. FTP-PET imaging may be helpful in predicting tau burden at autopsy in patients with underlying PiD neuropathology.

PiD is a neurodegenerative disease characterized by focal deposition of hyperphosphorylated 3-repeat (3R) tau in the brain. Molecular neuroimaging with various ligands, via PET, affords in vivo views of accumulated abnormal tau. The utility of one such ligand, flortaucipir ([^{18}F]AV-1451; FTP), in 3R-tauopathies is unclear, as autoradiography studies, expected to detect tau burden ex vivo, have found absent-to-minimal binding in PiD and other non-Alzheimer disease tauopathies.[2–5] Importantly, some studies have shown in vivo signal of unknown etiology. To date, no FTP-PET-autopsy studies have been published for 3R-tauopathies. This case assessed the relationship between FTP-PET uptake and (1) tau burden at autopsy and (2) measures of neurodegeneration from hypometabolism on [^{18}F]fluorodeoxyglucose (FDG) PET and atrophy on MRI. Correlative autoradiography was also performed.

Methods

The patient underwent neurologic, neuropsychological, speech, and language assessments, as previously described,[1] with 3T volumetric head MRI, and FDG, Pittsburgh Compound B (PiB), and FTP-PET scans. Data from the visit 13 months before death, with subsequent autopsy and autoradiography evaluation,[2] were utilized. She provided written consent to participate in this Mayo Clinic Institutional Review Board–approved study.

Tau burden at autopsy was abstracted as previously described.[6] FTP- and FDG-PET uptake and gray matter thickness for available regions of interest (ROIs) (amygdala, anterior cingulate, Broca area, middle frontal, orbitofrontal, inferior parietal, primary and supplementary motor, and anterior and superior temporal) were computed. To create standard uptake ratios (SUVRs), FTP-PET uptake in each ROI was divided by cerebellar crus gray matter uptake, and FDG-PET uptake was divided by the pons uptake. A global PiB SUVR was generated, with cerebellar crus gray matter as a reference region (amyloid positivity > 1.48). PET scans were coregistered to the MRI in SPM12. ROIs were localized using the Mayo Clinic Adult Lifespan Template atlas (nitrc.org/projects/mcalt/). Spearman rank correlations were calculated using JMP software (v.14.1.0), $\alpha = 0.05$.

Results

FTP-PET revealed increased signal across the right greater than left temporal and frontal lobes, the putamen, pallidum, amygdala, entorhinal cortex, and anterior cingulate. FDG-PET similarly

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demonstrated asymmetric, right greater than left, bilateral frontal, and anterior temporal lobe hypometabolism. Regions of reduced metabolism were noted in the regions with the highest FTP uptake (figure 1). The PiB-PET scan was negative, with a global SUVR of 1.30.

Regional FTP-PET SUVRs showed correlations with FDG-PET ($r = -0.88$, $p = 0.0008$), gray matter thickness ($r = 0.70$, $p = 0.0358$), and tau burden at autopsy ($r = 0.89$, $p = 0.0188$) across ROIs. FTP autoradiography revealed absent-to-minimal binding in areas where dense 3R-tau was observed on immunohistochemistry (figure 2).

Discussion

This study describes in vivo FTP-PET imaging and autoradiography in a case of autopsy-confirmed PiD. Moderate FTP uptake was seen, similar to previous in vivo reports[3,4]; the magnitude of uptake was comparable to that seen in 4R-tauopathies and lower relative to Alzheimer disease. Regional FTP uptake showed a strong correlation with underlying, quantitatively measured 3R-tau burden at autopsy, possibly mediated by stronger relationships with neurodegeneration. Although statistically significant, the relationship between FTP uptake and autopsy burden must be taken with caution, given the small areas sampled. Past research has yielded mixed findings in 4R-tauopathies, with a strong correlation between FTP-PET uptake and autopsy findings[6] and weaker[7] or absent[6] relationships between FTP-PET and other measures of neurodegeneration (e.g., atrophy).

There was absent-to-minimal displaceable autoradiography in regions with tau burden on immunohistochemistry, similar to past findings in both 3R- and 4R-taupathies.[2–5] Given the known tau burden at autopsy in this case, there is discordance between autoradiography and both autopsy and FTP-PET. Autoradiography may not wholly reflect FTP-PET results due to methodological decisions (e.g., tissue preparation methods) or contributions of perfusion to observed FTP signal.

Although limited by the sampling of 1 hemisphere due to standard operating procedures (less-affected left hemisphere), this study details the multimodal manifestation of the neuronal pathophysiology of PiD and provides insight into the relationship between in vivo FTP uptake and tau deposition at autopsy. Further research is needed to understand the relationship between FTP and 3R-tau pathologies and determine whether FTP is an appropriate biomarker for such tauopathies, particularly as uptake meaningfully reflected the clinical manifestation of PiD neuropathology in this case.

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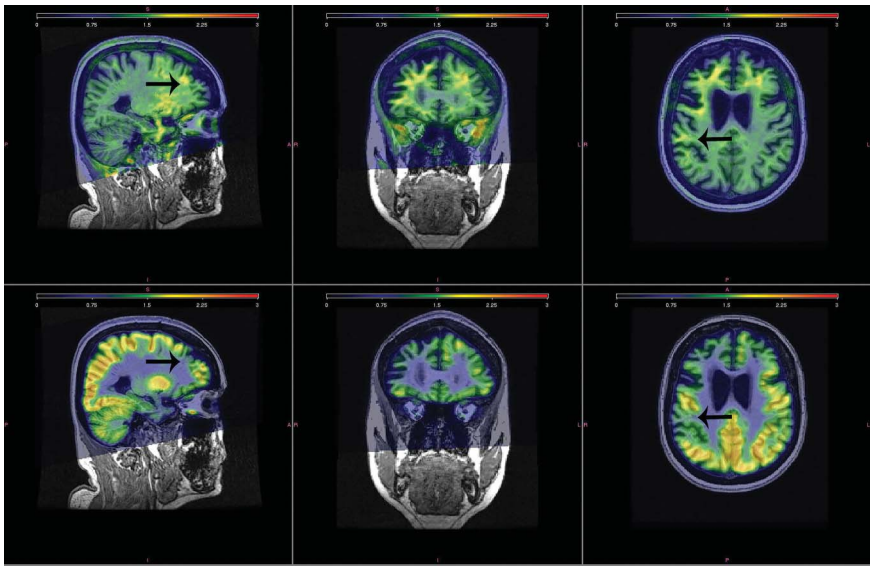
Figure 1 PET Scans



Top panel shows the triplanar view of the SUVR FTP-PET scan, highlighting uptake predominantly in the white matter. Analogous view of the SUVR FDG-PET scan is shown in the bottom panel, demonstrating reduced metabolism in corresponding regions with the highest FTP uptake (example noted with arrows). FDG = fluorodeoxyglucose; FTP = flortaucipir; SUVR = standard uptake ratio.

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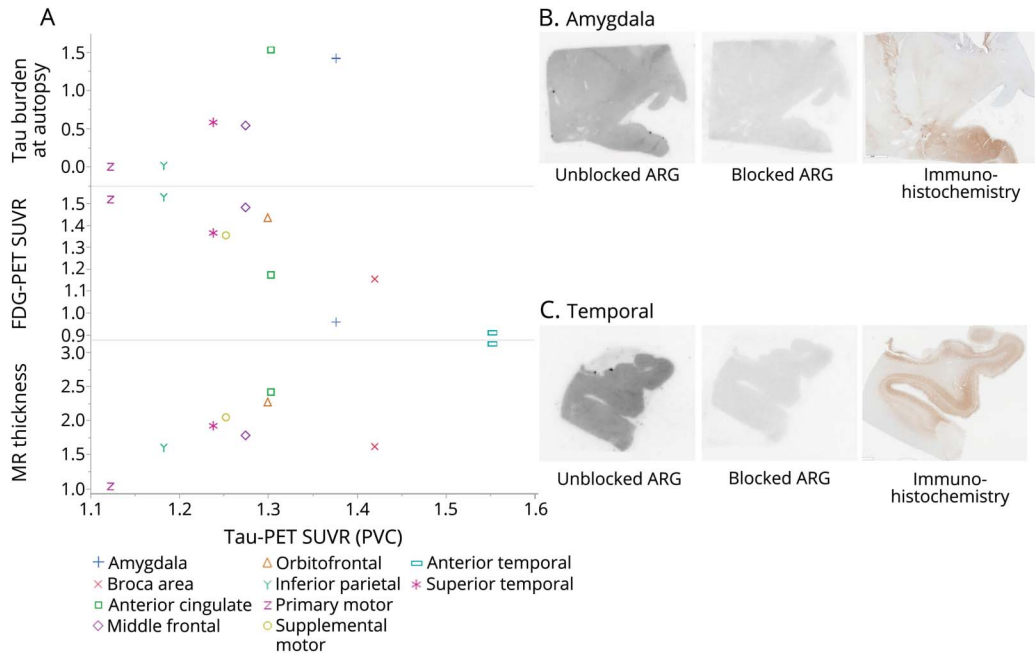
Figure 2 Immunohistochemistry, Autoradiography, and Scatter Plots of Relative Relationships



(A) Scatter plots of the relationship between FTP-PET SUVR (2-compartment partial volume corrected) and tau burden at autopsy, FDG-PET SUVR, and MR thickness in the available regions of interest. (B) ARG (unblocked and blocked) and correlative IHC with PHF-1 in the amygdala. There was absent-to-minimal displaceable ARG binding corresponding to regions where 3 R-tau burden was dense on IHC. (C) Similarly shows ARG and IHC with PHF-1 in the temporal region, where there was also absent-to-minimal displaceable ARG binding corresponding to regions where 3 R-tau burden was dense on IHC. Tau burden assessed with phospho-tau CP13; gift from Peter Davies. ARG = autoradiography; FDG = fluorodeoxyglucose; FTP = flortaucipir; IHC = immunohistochemistry; MR = magnetic resonance; SUVR = standard uptake ratio.

Disclosure

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Christopher G. Schwarz, PhD	Mayo Clinic, Rochester, MN	Conceptualization of the study, analysis of the data, and revision of the manuscript
Melissa E. Murray, PhD	Mayo Clinic, Jacksonville, FL	Acquisition of the data, analysis of the data, interpretation of the data, and revision of the manuscript
Jessica F. Tranovich, BS	Mayo Clinic, Jacksonville, FL	Acquisition of the data, review of the manuscript
Nancy E. Scott, MS	Mayo Clinic, Rochester, MN	Acquisition of data, analysis of the data, and revision of the manuscript
Val J. Lowe, MD	Mayo Clinic, Rochester, MN	Acquisition of the data, analysis of the data, interpretation of the data, and revision of the manuscript
Jennifer L. Whitwell, PhD	Mayo Clinic, Rochester, MN	Interpretation of the data and revision of the manuscript
Keith A. Josephs, MD, MST, MSc	Mayo Clinic, Rochester, MN	Conceptualization of the study, design of the study, interpretation of the data, and revision of the manuscript

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