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Tau PET in autosomal dominant Alzheimer disease: small windows, big picture

Eric M. McDade, DO and

Assistant Professor of Neurology, Washington University at St. Louis School of Medicine,
Associate Director, Dominantly Inherited Alzheimer Network Trials Unit, Phone: (314) 747-0725,
ericmcdade@wustl.edu

Randall J. Bateman, M.D.

Charles F. and Joanne Knight Distinguished Professor of Neurology (Bateman Lab), Director,
Dominantly Inherited Alzheimer's Network (DIAN) and Trials Unit (DIAN), Washington University
School of Medicine, 660 South Euclid Avenue, Box 8111, St. Louis, MO 63110,
batemanr@wustl.edu, Phone: 314-747-7066

The introduction of positron emission tomography (PET) tracers that can identify paired helical filaments of hyperphosphorylated tau, i.e. neurofibrillary tangles (NFT), has been met with tremendous optimism in the field of Alzheimer disease (AD) research. For example, a search in [PubMed.gov](https://pubmed.ncbi.nlm.nih.gov/) indicates that the number of publications related to “tau PET” has increased from 39 in 2010 to over 270 in the past two years, and tau PET scans are now being integrated into large observational and clinical trial studies. This optimism is based on the expectation that these tracers will provide a deeper understanding of the biology of the disease, and may also provide a surrogate biomarker measure that is related to the cognitive impairment of the disease.

What have we learned from Tau PET as a tool for the study of AD? First, the pattern of tau ligand binding identified in aging and with AD symptom progression, generally fits the topographical progression that was developed from post-mortem studies by Braak and Braak(1). The medial temporal lobe has been consistently identified as the first area of NFT accumulation in aging and also present in older populations with evidence of A β . However, the role of the medial temporal lobe as the initial site of NFTs in younger onset AD, including ADAD, is less clear. Additionally, there is evidence that presence of tau PET pathology outside the medial temporal cortex in AD is associated with the presence of amyloid plaque pathology(2, 3), suggesting that although the topographical distribution of these pathologies can be distinct, they remain critically related. Second, is that the development of cortical A β PET pathology clearly precedes that of cortical tau PET pathology (4–8). The finding that amyloid pathology precedes tau pathology was predicted based on AD animal model and genetics studies. Third, tau PET pathology topographic location correlates very strongly with clinical symptoms (2–4). This finding provides mechanistic insight into the cascade of events leading to cognitive decline and dementia and supports the possibility of tau PET pathology as a potential future surrogate biomarker for use in clinical trials.

However, these findings have been reported in cross-sectional studies, almost exclusively in late onset, sporadic AD. As a result, there are uncertainties, particularly in relation to the temporal lag between the onset A β pathology and the spread of tau PET pathology and the distinction between age related tau pathology (9) and that related to AD. With ongoing longitudinal studies in diverse groups of cohorts including younger and older ages of onset, these uncertainties will be resolved. The time lag between A β pathology and NFT pathology is important for clinical trial design in AD. For example, questions such as ‘what stages of AD should A β and tau directed therapeutics be started?’ need to be addressed. In this issue of JAMA Neurology, Quiroz and colleagues report an approach to help address this and other questions by studying tau PET in a group of young participants that are destined to develop Alzheimer’s disease dementia, i.e. autosomal dominant AD (ADAD)(10).

ADAD offers the advantage of a predictable time when symptom onset and dementia is likely to start and thus a point of reference relative to the onset of AD related pathologies. By studying participants at different relative times in the preclinical period, longitudinal estimates can be made from a construction of cross-sectional data. In this reported study, 12 mutation carriers (9 cognitively normal) and 12 age and gender matched mutation non-carriers (age range 28–55 years old) from a large, well characterized cohort of the *PSEN1* E280A mutation from the Antioquia, Colombia region underwent A β (C11-PIB), tau PET (18-F Flurtaucipir) and neuropsychological testing. Importantly, the volunteers for this study ranged from more than 20 years before estimated symptom onset through mild dementia.

Similar to previous studies in this group of participants (11), they found that cortical amyloid begins to develop at least 15 years before dementia. Not surprisingly, they found no evidence of tau pathology in the non-carriers, regardless of age. Interestingly, they found that in one mutation carrier, tau PET pathology in the medial temporal-entorhinal cortical area began to develop 6 years before estimated onset of clinical symptoms, suggesting at least a 10-year gap between A β and tau PET pathologies. In contrast, prior findings of CSF measures of tau and p-tau are increased much earlier, as early as 15 years before estimated symptom onset (11).

Another important finding was that in ADAD mutation carriers, tau PET pathology in the medial temporal lobe structures remained at levels similar to non-carriers (none present) if cortical A β levels did not exceed the threshold for being “positive”. This suggests in ADAD, like sporadic AD, that A β pathology likely plays a role in facilitating tau pathology. Further, there was evidence that the highest tau PET amounts were found in those with the highest A β plaque pathology. In contrast to findings in late onset sporadic AD, there was not pre-existing pathology in the medial temporal lobes without A β pathology.

Lastly, the authors looked at the relationship between A β and pathology as it relates to cognitive performance in verbal memory and the mini mental state examination and found no relationship with A β and a correlation with tau PET pathology. However, given the small number of symptomatic participants, the strength of these associations are not strong and require additional study at different stages of disease.

The study by the authors makes substantial contributions, which address important questions about when tau PET pathology develops. These findings are complimentary and supportive of ongoing studies from the Dominantly Inherited Alzheimer Network (12) which also found that the development of tau PET pathology is closely linked to the onset of symptoms. More recent reports from the DIAN study (n=50) have indicated a remarkable link between symptom onset and the presence of tau pathology(13), long after CSF tau changes have begun. Taken together, these findings suggest a modified pathobiological cascade of AD with CSF tau changing ten to fifteen years before tau pathology begins (figure 1).

Several important conclusions come from tracking tau pathology in early onset ADAD. First, is the evidence that CSF tau and p-tau levels are not equivalent to tau PET measures of pathology. In contrast to commonly held assumptions, the discrepancy between when CSF tau is increased many years before when tau PET is increased suggests that there are likely important differences. This is consistent with the fact that tau protein fragments are structurally different proteins in CSF versus in the aggregated pathology form. The soluble forms are truncations that do not have the repeat domains found in pathological aggregates(14). Second, the findings in tau pathology in ADAD highlights the need to combine complimentary orthogonal measures of AD including CSF biomarkers and neuroimaging measures of tau and A β pathology, metabolism (FDG PET), structural (MRI), functional connectivity and other AD specific biomarkers. This will be particularly important in understanding how therapies that target the pathologies of tau and A β will impact the cascade of AD. Ultimately, these questions will be best answered by comparing and contrasting both ADAD and sporadic AD in comprehensive observational studies and clinical trials.

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Figure 1.

A β and Tau biomarker trajectories in autosomal dominant AD.

Approximate trajectories of amyloid beta (CSF and PET) and tau (CSF and PET) from cross-sectional studies in the DIAN and the E280A Colombian kindred. Based on prior studies and the current study by Quiroz *et al.*, there is evidence of a period of approximately 10 to 15 years between the increase in soluble tau and neurofibrillary tangle pathology in the presymptomatic period.