

The exception makes the rule

Not all A β plaques are created equal

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Neurology® 2012;79:206–207

It is now established that the neuropathology of Alzheimer disease (AD) accumulates many years before the expression of overt symptoms. The development of β -amyloid (A β) binding ligands that allow identification of A β pathology in vivo using PET has enabled identification of persons harboring these changes. Though there are still unanswered questions regarding the specific prognostic value of a positive A β scan (e.g., what symptoms will develop over what time frame), use of A β imaging to facilitate secondary prevention trials for AD is being pursued.

In this issue of *Neurology*®, Schöll et al.¹ draw attention to a limitation of A β imaging in early onset familial AD (eoFAD). Using PET imaging with Pittsburgh compound B (PiB), they showed that 2 carriers of the E693G substitution in the *APP* gene (the “Arctic mutation” or *APP*_{arc}), which is fully penetrant for eoFAD, lacked detectable PiB retention. This was distinct from the positive PiB pattern seen in 2 persons carrying other eoFAD mutations and in 7 patients with sporadic AD, but was similar to the negative PiB scans seen in 5 noncarriers from families with the *APP*_{arc} mutation and 7 healthy controls. Both subjects with the *APP*_{arc} mutation had fluorodeoxyglucose PET and CSF evidence (diminished A β ₄₂, elevated t-tau and p-tau) of AD. One subject additionally had brain atrophy evident on MRI and moderate to severe cognitive impairment qualifying this patient for a diagnosis of dementia. The lack of PiB binding described with the *APP*_{arc} mutation by Schöll et al. could be related to the atypical plaque morphology previously demonstrated neuropathologically in a family member dying with this mutation,² specifically, ring-like plaques lacking a congophilic core. The unusual nature of the plaques may be related to the manner in which mutations within the sequence of APP may cause disease, that is, by altering the assembly properties and catabolism of A β .

Interpreting a negative result is a perilous endeavor. As the authors attest, there are various expla-

nations for the lack of PiB binding in these subjects, including affinity of PiB for other moieties not present in the pathology associated with *APP*_{arc}. While there is usually a positive correlation between A β burden as measured by PiB PET and brain A β at postmortem or biopsy,³ there have been additional persons reported with negative PiB scans in whom AD pathology was either likely or present. Similar to the findings by Schöll, a group in Japan⁴ reported a novel *APP* mutation (the “Osaka” mutation, Δ E693) in which a PiB study showed low cortical retention. The authors reported that the Osaka A β peptide did not form fibrils but subsequent studies revealed that the mutant peptide did indeed form fibrils, and at a rate 400-fold greater than that of wild-type A β .⁵ These assemblies were more compact than those formed by wild-type A β , suggesting that binding site accessibility might explain negative amyloid ligand binding.

Investigators correlating PiB binding and frontal lobe A β burden in subjects undergoing intraventricular monitoring for normal pressure hydrocephalus revealed 1 patient (out of 6) with plaques who had a PiB scan in which the A β burden was below the AD cutoff.⁶ A Washington University team⁷ reported a longitudinally characterized subject with a negative PiB scan at age 88.5 years with evidence of cognitive decline and CSF biomarker evidence for AD pathology at age 89.5. At the time of his death at age 91, diffuse A β plaques were found, though only minimal neuritic plaques and neurofibrillary tangles were present. In the context of his declining cognitive function and abnormal CSF findings, an incipient process representing AD was likely, yet PiB retention was below the threshold to be considered “positive.” These cases further support the hypothesis that different “conformations” of A β deposits⁸ affect the binding patterns of tracers and that A β imaging may not recognize all types of A β deposits with equal sensitivity.^{9,10} However, the numbers of these cases appear to be small at this point.

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A β imaging is an important step forward in identifying A β pathology in humans in vivo in a relatively noninvasive way, though there is much to be learned regarding the implications of a positive A β scan in asymptomatic persons. Furthermore, the report by Schöll et al. brings attention to a limitation of A β imaging—the potential for false-negative scans due to atypical A β assembly structure or plaque organization. In demonstrating the lack of concordance between PiB signal and other biomarkers in a subset of persons with AD, the authors have underscored the diversity of the pathology that can underlie the “Alzheimer diseases,” the full spectrum of which we must better comprehend if we are going to diagnose and treat them optimally.

DISCLOSURE

J. Ringman receives research support from an Alzheimer’s Disease Research Center grant (AG016570) and the Dominantly Inherited Alzheimer Network (AG-032438) from the National Institute on Aging and the Jim Easton Consortium for Alzheimer’s Disease Drug Discovery and Biomarkers at UCLA and has received compensation as an advisory board member for Takeda Pharmaceuticals and StemCells, Inc. D. Teplow receives research support from NIH grants AG016570, NS038238, AG 041295, and the Jim Easton Consortium for Alzheimer’s Disease Drug Discovery and Biomarkers at UCLA. V. Villemagne receives research support from grants 566614, 630489, and 1011689 from the National Health and Medical Research Council of Australia, Alzheimer’s Drug Discovery Foundation Research Grant of the USA (20101208 AFTD), and a New Energy and Industrial Technology Development Organization (NEDO) grant of Japan, and is a consultant for Bayer Healthcare. **Go to Neurology.org for full disclosures.**

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