Title
The exception makes the rule

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The exception makes the rule

Not all Aβ plaques are created equal

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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 (Aβ) binding ligands that allow identification of Aβ 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 Aβ scan (e.g., what symptoms will develop over what time frame), use of Aβ 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 Aβ 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 Aβ42, 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 Aβ.

Interpreting a negative result is a perilous endeavor. As the authors attest, there are various explanations 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 Aβ burden as measured by PiB PET and brain Aβ 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 Japan[4] reported a novel *APP* mutation (the "Osaka" mutation, ΔE693) in which a PiB study showed low cortical retention. The authors reported that the Osaka Aβ 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 Aβ.[5] These assemblies were more compact than those formed by wild-type Aβ, suggesting that binding site accessibility might explain negative amyloid ligand binding.

Investigators correlating PiB binding and frontal lobe Aβ 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 Aβ burden was below the AD cutoff.[6] A Washington University team[7] 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 Aβ 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 Aβ deposits[8] affect the binding patterns of tracers and that Aβ imaging may not recognize all types of Aβ deposits with equal sensitivity.[9,10] However, the numbers of these cases appear to be small at this point.

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Aβ imaging is an important step forward in identifying Aβ pathology in humans in vivo in a relatively noninvasive way, though there is much to be learned regarding the implications of a positive Aβ scan in asymptomatic persons. Furthermore, the report by Schöll et al. brings attention to a limitation of Aβ imaging—the potential for false-negative scans due to atypical Aβ 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

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