When There's No Amyloid, It's Not Alzheimer's

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Reporting in the August 24 JAMA Neurology online, researchers led by Eric Reiman at Banner Health in Phoenix, confirm what others have suspected from PET imaging, namely, that as many as one-third of the people clinically diagnosed with mild to moderate Alzheimer's disease do not meet criteria for significant amyloid accumulation in the cerebral cortex. Reiman and colleagues came to this conclusion after examining brain tissue postmortem—the gold standard for assessing amyloid burden. The finding puts the kibosh on the idea that some PET scans are negative because amyloid ligands bind poorly to particular forms of amyloid in some AD patients. It also reinforces questions about the accuracy of clinical diagnoses of AD and leaves the field struggling to explain what causes dementia in these amyloid-negative individuals. This promises to be an intense area of investigation, said Reiman.

With the advent of ligands suitable for in vivo PET imaging of β-amyloid in the brain, researchers began to notice something did not quite fit their expectations. Surprisingly, in large Phase 3 clinical trials of people with mild to moderate Alzheimer's disease, about one-third of ApoE4-negative patients tested negative for brain amyloid. Around 13 percent of ApoE4 carriers also seemed to have escaped Aβ pathology (see Jan 2014 news). The Alzheimer's Disease Neuroimaging Initiative delivered similar numbers. " We wondered if there was an underestimate [of amyloid] because of low affinity binding of PET ligands to diffuse plaque, or if those patients had predominantly soluble amyloid in the brain," said Reiman.

To find out, first authors Sarah Monsell from the National Alzheimer's Coordinating Center, University of Washington, Seattle, surveyed people who had a clinical diagnosis of mild to moderate AD and had come to autopsy within two years of their last visit to an Alzheimer's Disease Research Center. By sheer coincidence, between September 1, 2005, and September 1, 2012, exactly 100 ApoE4 carriers and 100 non-carriers met those criteria.

Of the ApoE4 non-carriers, 37 had minimal neuritic plaques on autopsy and 28 had neither neuritic nor diffuse plaques. From those 37, Monsell obtained sufficient brain tissue to measure soluble and insoluble Aβ by ELISA. She found two patients with moderate levels of total Aβ and none with levels typically found in patients with neuropathological AD. Autopsies of the 100 ApoE4 carriers revealed 13 with no or only sparse neuritic plaques, and four free of either neuritic or diffuse plaques. ELISAs on tissue obtained from three of the 13 indicated low levels of soluble and total Aβ, again, much less than typically seen in patients with pathologically confirmed diagnosis of AD.

"All told, this suggests to us that 25 percent of all patients with a clinical diagnosis of AD have no appreciable amyloid in the brain," said Reiman. Earlier, researchers led by Tom Beach at Banner Sun Health Research Institute, Sun City, Arizona, and Walter Kukull at the NACC had reported that about 17 percent of patients diagnosed with AD did not meet pathological criteria for the disease, but they had not broken that data down by ApoE4 status. Researchers led by Bradley Hyman at Massachusetts General Hospital, Charlestown, reported similar findings, though they did not test for soluble Aβ (see Beach et al., 2012; Serrano-Pozo et al., 2014).

If not AD, then what caused the cognitive decline in these patients? The authors looked for signs of other neuropathologies. Sixteen of the 37 amyloid-free ApoE4 non-carriers had evidence of neurofibrillary tangles (Braak stage III-VI), suggesting their dementia may be a tau-only form. However, in a post hoc analysis of age-matched normal controls, 35 percent had similar Braak staging in the absence of any cognitive decline. The other ApoE4 non-carriers had neuropathological signs of hippocampal sclerosis, Lewy body disease, and frontotemporal lobar degeneration, among other disorders. Reiman said whether tau or some other pathology explains their cognitive decline remains to be determined. "We need to better characterize these patients to see how they compare in terms of clinical features, underlying risk factors, and progression," he told Alzforum.

The 25 percent of patients diagnosed with mild to moderate AD who turn out to have no brain amyloid uncannily resemble the quarter of healthy older controls who likewise have no sign of brain amyloid but test positive for markers of neurodegeneration. Researchers are only just beginning to characterize these cases of suspected non-Alzheimer pathophysiology (SNAP). Their neurodegeneration appears to progress very slowly, if at all (see Sep 2015 conference news). In an accompanying editorial, Stephen Salloway, Butler Hospital, Providence, Rhode Island, and Reisa Sperling, Brigham and Women's Hospital, Boston, note that there are fewer ApoE4 carriers among people with SNAP than among those with amyloid pathology. Monsell also found that people who were clinically diagnosed with mild to moderate AD but amyloid-negative were more likely to be ApoE4-negative. How SNAP relates to these patients remains to be seen, said Reiman.

"The implication for now is that if you are studying an anti-amyloid treatment in someone with mild to moderate AD or mild cognitive impairment, then it makes sense to look for amyloid pathology first," said Reiman. Salloway and Sperling noted that, "Distinguishing between AD and non-AD pathologies will become increasingly important as more targeted treatments become available for intervention in the preclinical and early clinical stages of AD." —Tom Fagan

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REFERENCES

News Citations

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