Amyloid and neurodegeneration

Converging and diverging paths

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Since the first report of amyloid imaging with Pittsburgh compound B (PiB), special attention has been given to the individuals who, though cognitively normal by testing, have substantial amounts of fibrillar β-amyloid (Aβ) pathology in their brain.[1] This state, previously predicted by several postmortem studies,[2] is also the focus of research criteria for preclinical Alzheimer disease (AD).[3] With these criteria, the pathophysiologic spectrum of AD was stretched past the earliest clinically detectable stages such as mild cognitive impairment (MCI)[4] to include cognitively normal individuals who show evidence of brain amyloid deposition by CSF analysis or amyloid PET. This concept of preclinical AD currently forms the foundation of a trial aimed at preventing the emergence of AD in amyloid-positive individuals—the Anti-Amyloid Treatment of Asymptomatic Alzheimer's Disease (A4) trial.[5] Clearly, it is important to understand this state of asymptomatic β-amyloidosis as fully as possible.

The report by Jack et al.[6] in this issue of *Neurology*® adds important new information by focusing on the very beginnings of Aβ pathology in incident amyloid-positive subjects (defined by PiB PET), thereby increasing our understanding of clinically asymptomatic β-amyloidosis. First, they find that the incidence rate is approximately 13% per year among 123 cognitively normal individuals between the ages of 74 and 82 years. This incidence rate is very likely related to age and *APOE* ε4 carrier status, just as the prevalence of amyloid positivity is.[7,8] Second, the investigators looked for baseline characteristics that were associated with incident amyloid positivity an average of 2.5 years later. Baseline default mode network connectivity was greater in the incident amyloid positivity group. This may be a reflection of the greater brain reserve necessary to remain in the cognitively normal state in the face of impending amyloid deposition or existing subthreshold amyloid deposition. In contrast, demographics, cerebral metabolism, hippocampal volume, and overall cognition were not different in the incident amyloid positivity group.

In this context, the role of the reserve proxies such as education and occupation should be considered in further studies of these amyloid-positive but cognitively normal individuals, since molecular PET imaging has shown that higher education is associated with functional brain reserve in AD and MCI, which masks the clinical expression of neurodegeneration.[9,10]

In light of the assumptions built into the research criteria for preclinical AD,[3] an interesting observation of Jack et al. involves the relative timing of the emergence of asymptomatic β-amyloidosis and the presence of markers of neurodegeneration, namely, abnormal cerebral metabolism or hippocampal atrophy. The preclinical AD criteria only encompass characteristics of the pathway to clinical AD (not other causes of cognitive impairment) and presume that amyloid deposition precedes neurodegeneration and that both occur before the first emergence of subtle, subclinical cognitive deficits. However, in the present study, 42% of the incident amyloid-positive group had at least one marker of neurodegeneration before they had amyloid deposition detectable by PiB PET. This could be an underestimate if more sensitive methods of detecting cerebral metabolic abnormalities with FDG-PET were employed.[11] Importantly, hippocampal atrophy and cerebral hypometabolism may not be interchangeable markers of neurodegeneration, suggesting the value of identifying specific brain metabolic markers of neurodegeneration, especially for future clinical trials that target the so-called suspected nonamyloid pathophysiology (SNAP) population.

A "neurodegeneration first" pathway could relate to a possible insensitivity of PiB PET to detect the earliest events of amyloid deposition that might already be causing this neurodegeneration. However, some individuals must be on a pathway to non-amyloid-based neurodegeneration and therefore be representative of SNAP.[12] Amyloid deposition might be relatively unimportant in these individuals who would develop a non-AD dementia (e.g., frontotemporal or Lewy body dementia) before any Aβ-mediated neurodegeneration could occur.

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The numbers become small when divided in this way, but several "sanity checks" can be performed. First, if 13% of people age 70–80 are amyloid-positive and if a large majority will go on to develop AD via MCI (and a minority are developing other dementias with incidental amyloid positivity), then the incidence of MCI should be near this same proportion in a carefully observed population. Interestingly, Roberts et al.[13] have published the incidence rates of MCI in this same Olmsted County cohort and found an incidence of ~9% at age 80–84 and ~13% at age 85–89. Of course, only about two-thirds of clinically diagnosed patients with MCI have amyloid deposition,[14] but overall, it appears that the numbers make sense.

The big question that remains is whether individuals with asymptomatic β-amyloidosis are those who develop amyloid-positive MCI and then clinical AD. The study by Jack et al. lends evidence that they are, while also pointing out that while amyloid and neurodegeneration can converge on the path to AD, they may also diverge on pathways to non-AD dementias.

AUTHOR CONTRIBUTIONS

William E. Klunk: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision. Daniela Perani: drafting/revising the manuscript.

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DISCLOSURE

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