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EDITORIAL

Do subtle cognitive deficits precede amyloid accumulation?

Cart before the horse

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Objective subtle cognitive difficulties predict future amyloid accumulation and neurodegeneration
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Over the last decade, a hypothesized model of dynamic sequential biomarker changes dominated the Alzheimer disease (AD) research field. The model, informed by the amyloid hypothesis,[1] proposed a prototypical cascade, lasting up to decades, in which brain β-amyloid initiates acceleration of tau pathology, which in turn drives neurodegeneration and associated cognitive symptoms. In this issue of *Neurology*®, Thomas et al.[2] tested the specific hypothesis that if amyloid deposition occurs long before downstream detectable effects on cognition, the presence of cognitive deficits should not precede accumulating rates of amyloid deposition. They found, however, that they do: in a large cohort of older adults without dementia, a subgroup with objectively defined subtle cognitive difficulties identified on neuropsychological testing at baseline showed increasing brain amyloid deposition on PET imaging over 4 years, despite having baseline amyloid levels that were similar to those characterized as cognitively normal. This subgroup also showed faster entorhinal cortical thinning compared to those without subtle cognitive difficulties. By comparison, participants with frank, though mild, cognitive impairment did not show faster amyloid accumulation relative to cognitively normal individuals but did have faster entorhinal cortical thinning and hippocampal atrophy over 4 years, consistent with Braak-staged spreading of tau neuropathology.[3]

There are other empirical challenges to the simple version of an amyloid-first model of the AD pathway. In postmortem samples, there is compelling evidence that intraneuronal tau pathology develops many years prior to amyloid plaques.[4] Further, 15%–30% of cognitively unimpaired older adults show biomarker evidence of neurodegeneration in the absence of substantial amyloidosis. This biomarker amyloid-negative but neurodegeneration-positive state poses higher risk for both cognitive decline and transition to amyloid positivity compared to older adults without either biomarker.[5] Co-occurring pathologies outside of the prototypical hypothesized AD cascade are the rule in postmortem studies and include vascular lesions, Lewy body pathology, and TDP-43.[6] Failed high-profile antiamyloid trials have invigorated reexamination of assumptions and compelled consideration of alternative hypotheses about AD pathogenesis and viable therapeutic targets.[7] There is an increasing reckoning of the complexity and heterogeneity of the disease. The 2018 National Institute on Aging–Alzheimer's Association Research Framework[8] proposed a structure for AD studies that (1) describes cognitive staging independently from biomarker profiles and (2) allows for expansion to additional biomarkers as they become available. While the framework has some flexibility and provides common nomenclature for researchers to test hypotheses, it is rigid in its requirement that evidence of current amyloidosis defines the Alzheimer continuum. Falsifiable hypotheses, such as the one put forth in Thomas et al., are critical to progress in the field, and ultimately to finding effective interventions. Indeed, the results of this study challenge prevailing models of both the initiating role of amyloid and the requirement of biomarker evidence of amyloid for defining the Alzheimer continuum.

A second important point in the Thomas et al. article is the demonstration that subtle objective cognitive deficits can be measured reliably and predict important biological changes associated

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with AD. Despite the recent emphasis on characterizing AD based on biomarker profiles alone, it is critical to emphasize that it is the cognitive deficits and associated functional impairment that are most problematic for patients and their families, and, as illustrated in the Thomas et al. study, highly predictive of the course of the disease. There is thus a great need to continue to focus on cognition, including the implementation and development of methods that push the boundaries of early detection. This goal can be achieved through the creation of new or modified instruments[9,10] and by exploiting fully the richness of data collected through traditional neuropsychological tests. Thomas et al. creatively utilized process scores of a common list-learning paradigm, reflecting specific measures of learning slope, retroactive interference, and recall errors, metrics not typically included in observational research related to AD. Broadly, new and alternative cognitive assessment strategies will be especially useful if they are also suitable for clinical prevention trials, as sensitive outcome measures of cognitive change, or for risk screening when disease-modifying treatments become available.

Several limitations of Thomas et al. are worth bearing in mind. The findings are not a strong refutation of the amyloid-first model as baseline amyloid levels were numerically, albeit not statistically, higher in the group with subtle cognitive difficulties, suggesting the possibility that the start of fibrillar or perhaps soluble forms of β-amyloid may have preceded or coincided with cognitive deficits. Also unknown is whether such subtle cognitive issues represent long-term, trait-like vulnerabilities or more recent decline. Future longitudinal studies will no doubt include tau and other relevant biological information, incorporating rates of change in biomarkers and cognition to further develop, test, and refine AD pathophysiologic models. Finally, as the authors note, the data were collected in the Alzheimer's Disease Neuroimaging Initiative, with participants who were largely highly educated, white, and generally healthy. This demographic homogeneity poses important limits to generalizability of the findings. Replication is needed, and particularly in participants from more population-representative cohorts. Such directions are critical to broaden applicability of AD neuroimaging and biomarker research beyond the highly screened and selected few who participated to more inclusive and diverse populations.[11]

Thomas et al. illustrate important components to advancing understanding of early AD pathways, if incompletely, as with any single study. Most critically, there is no progress without putting our best models to the cleverest tests.

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