Is dominantly inherited Alzheimer disease a clone of sporadic Alzheimer disease?

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Is autosomal dominant Alzheimer disease (ADAD) a good model for understanding sporadic late-onset AD (SpAD)? On the face of it, the answer seems obvious, but are appearances deceiving? The similarities between ADAD and spAD are many.[1] Until recently, the study of individuals with spAD was limited to the symptomatic phase of the disease or to the retrospective review of antecedent events in persons diagnosed with spAD. An invaluable advantage of studying ADAD has been the ability to identify persons at risk while they are not yet symptomatic and to relate the findings to their expected age at symptom onset.

Most early reports of the clinical and pathologic features of ADAD were case series, including the one in which Alzheimer disease was first discussed in *Neurology*®.[2] There are 90 identified families worldwide with mutations in the amyloid precursor protein, 405 identified families with mutations in presenilin1, and 22 identified families with mutations in presenilin 2.[3] ADAD constitutes much less than 1% of persons with symptomatic AD dementia. Because of the rarity of ADAD, special efforts were needed to assemble ADAD carriers for study. In 2009, the Dominantly Inherited Alzheimer Network (DIAN) was initiated and began recruiting individuals who came from families with ADAD. All participants underwent a series of biomarker studies aimed at characterizing the levels of brain β-amyloidosis and neurodegenerative status.[4] In the current issue of *Neurology*, the DIAN team reports relationships between β-amyloid levels measured with Pittsburgh compound B (PiB) PET and cognitive functioning.[5]

Wang et al.[5] studied asymptomatic ADAD carriers who were estimated to be about 12 years from their expected age at onset. Their mean age was 35 ± 9 years. The authors report that PiB-PET standardized uptake value ratio (SUVR) was not related to baseline cognitive status, but in longitudinal observations averaging 2.3 years, baseline β-amyloid burden was related to decline in memory. Even in longitudinal analyses, other cognitive functions were not related to baseline brain β-amyloid status. In contrast, in symptomatic ADAD carriers, who were 10 years older, baseline PiB-PET SUVR correlated with both baseline cognitive status and rate of decline in cognition in multiple domains.

The authors were careful in their conclusions to avoid ascribing direct causality to β-amyloid levels, but readers might not appreciate the need for caution. β-amyloidosis is not the proximate actor upon cognition.[6] There is an intermediary: neurodegeneration. Neurodegenerative changes—whether measures of cortical volume, neurofibrillary tangle changes, neuronal loss, synaptic dysfunction, or others—are much more closely correlated with cognition.[6,7] Cognitively normal individuals can harbor a high burden of β-amyloid, and in persons with AD dementia, cognitive decline is not correlated with β-amyloid burden. By the time ADAD mutation carriers are symptomatic, neurodegenerative changes are well established,[4] just as they are in spAD.[7] Therefore, the associations reported by Wang et al. actually reflect the extent to which β-amyloid levels drove critical neurodegenerative processes and how these processes in turn drove cognition.

The associations between β-amyloid levels and longitudinal cognitive decline in asymptomatic at-risk ADAD mutation carriers were to be expected even though the ADAD mutation carriers were many years away from symptomatic disease. This interpretation suggests that there should also have been an association between β-amyloid and cognition at baseline, and indeed the memory test score declines in asymptomatic carriers at baseline were in the right direction, although they were not significant. Because the cognitive changes in asymptomatic carriers were very small and the period of observation too short, the analyses were likely compromised by reduced power. In any case, because of the complexities of a serial relationship like β-amyloidosis → neurodegeneration → cognitive decline, more insights into each step are necessary to fully understand the link between β-amyloid levels and cognition.

The β-amyloid–cognition associations in ADAD are similar to those seen in SpAD. There are typically weak associations in asymptomatic individuals.[8] In symptomatic persons in the AD pathway, whether spAD[9] or ADAD, the presence of β-amyloidosis has

See page 790

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been strongly associated with cognitive decline. These associations are consistent with models of the pathogenesis of AD—both ADAD and spAD—in which medial temporal neurodegenerative changes intensify and spread into isocortex, apparently under the influence of β-amyloidosis[7] as the disease moves from asymptomatic to symptomatic stages.

Yet despite the parallels between ADAD and spAD in β-amyloid associations with cognition, the relationship between β-amyloid and neurodegeneration differs between ADAD and spAD in at least one critical way. The large difference between ADAD and spAD in age at onset implies that the neurodegenerative changes that drive cognitive decline must occur much younger in ADAD than in spAD. In spAD, medial temporal tauopathy appears in young adulthood and increases in abundance with advancing age. There is strong evidence that medial temporal tauopathy antedates the appearance of β-amyloid[10–12] and is not created by β-amyloidogenic mechanisms.[10–12] If ADAD and spAD are truly manifestations of one common chain of events, ADAD-induced β-amyloidosis must initiate or accelerate medial temporal tauopathy far earlier than occurs in the absence of ADAD mutations. But if that is true, β-amyloidosis in ADAD has a far more pernicious role in medial temporal tauopathy than is the case in spAD. The initiation of β-amyloid–induced neurodegeneration in ADAD is a different mechanism from the pre–β-amyloid medial temporal neurodegeneration that occurs in spAD.

Investigations in ADAD, as exemplified by the current report, have a unique capacity to inform us about disease mechanisms in AD. With the availability of imaging biomarkers for AD, it is now possible to compare and contrast asymptomatic and very early symptomatic ADAD and spAD using identical biomarker methods. We are no longer in the position of having to rely exclusively on clinical observations and postmortem reconstructions to address the similarities and differences between ADAD and spAD.

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DISCLOSURE

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