ALZHEIMER DISEASE

Alzheimer dementia with sparse amyloid—AD mimic or variant?

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Refers to Monsell, S. E. *et al.* Characterizing apolipoprotein E ε4 carriers and noncarriers with the clinical diagnosis of mild to moderate Alzheimer dementia and minimal β-amyloid peptide plaques. *JAMA Neurol.* http://dx.doi.org/10.1001/jamaneurol.2015.1721

In a new study, one-quarter of individuals with a clinical diagnosis of mild to moderate Alzheimer dementia had no or only sparse neuritic amyloid plaques in their brains, and most were also at a low or an intermediate neurofibrillary tangle stage. The findings have enormous implications for clinical trials of anti-amyloid-β and anti-tau therapies.

Alzheimer disease (AD) is defined by the widespread presence of extracellular plaques, formed from amyloid-β (Aβ) peptide, and intracellular neurofibrillary tangles, consisting of hyperphosphorylated tau (p-tau), in the cerebral cortex. In a clinicopathological study published recently in *JAMA Neurology*, Monsell and colleagues[1] aimed at characterizing a subset of patients who had received a clinical diagnosis of probable AD, but exhibited 'insufficient' amyloid plaque burden in their brain to warrant a definite pathological diagnosis of AD.

The new study is pertinent, because concerns were recently raised in the AD research community over the finding that up to 16% of individuals with a clinical diagnosis of mild to moderate probable AD (Mini-Mental State Examination [MMSE] score 16–26), enrolled in a phase III trial of anti-Aβ immunotherapy, actually had a negative amyloid PET scan at baseline.[2] So, what is the pathological substrate of these AD 'phenocopies'? Do these individuals have another underlying disease mimicking the clinical expression of AD, or do they have a pathological variant of AD? Have the clinical trials conducted so far been adequately powered to account for this subset of patients? If not, could this be the explanation for the failure of some AD drug discovery programmes?

Monsell *et al.*[1] analysed the autopsy cohort of the National Alzheimer's Coordinating Center (NACC), a multicentre, longitudinal cohort study of ageing that is ongoing at 34 Alzheimer's Disease Centers across the USA. The investigators selected study participants who had died within 2 years of the last clinical evaluation, had a clinical diagnosis of probable AD and a MMSE score between 16 and 26, had consented to an autopsy, and had an apolipoprotein E (*APOE*) genotype available. The authors first stratified the sample by *APOE* status into *APOE*ε4* carriers ($n = 100$) and noncarriers ($n = 100$). The *APOE*ε4* allele is the strongest genetic risk factor for the development of AD, and is thought to promote the accumulation of Aβ peptide by impairing its clearance from the brain. The CERAD (Consortium to Establish a Registry for Alzheimer's Disease) score of neuritic plaques was used to stratify each group according to amyloid plaque burden, thereby creating two categories: none to sparse, and moderate to frequent. Of note, studies correlating *in vivo* PET quantification of amyloid deposition with postmortem examination of the same individuals have shown that the amyloid PET radiotracers are specific for dense-core fibrillar (usually neuritic) plaques, but do not detect diffuse (usually non-neuritic) Aβ deposits, and that individuals with no or sparse neuritic plaques are expected to have a negative amyloid PET scan.

Of the 100 *APOE*ε4* noncarriers included in the study,[1] 37 had no or sparse neuritic plaques, and only six of these 37 had moderate or frequent diffuse amyloid plaques. By contrast, only 13 of the 100 *APOE*ε4* carriers had no or sparse neuritic plaques, although the majority of these (nine of 13) had moderate or frequent diffuse plaques. Because of the known effects of the ApoE4 isoform on Aβ levels, as described above, these different proportions of neuritic and diffuse plaques between genotypes are expected. Regardless of the *APOE* genotype, most of the study participants were at low (0–II) or intermediate (III–IV) Braak stages with regard to neurofibrillary tangles.

These results largely concur with our previous study in the same cohort.[3] Besides stratification by *APOE*ε4* status, a novelty of the present study[1] resides in the addition of biochemical quantification of soluble and insoluble Aβ. The authors had access to frozen samples from 19 of the 37 *APOE*ε4* noncarriers and three of the 13 *APOE*ε4* carriers. Contrary to typical observations in patients with a definite pathological diagnosis of AD, none of these individuals had high levels of soluble or insoluble Aβ, further arguing against a causative role for Aβ in dementia in these patients. *APOE*ε4* can induce both oligomerization of Aβ and synaptic localization of Aβ oligomers. Given the low number of *APOE*ε4* carriers in the study, and the fact that neither oligomeric Aβ species nor synapse-enriched preparations were assayed, the possibility remains that the mild to moderate dementia in *APOE*ε4* carriers with no or sparse neuritic plaques is driven, at least in part, by synaptotoxic soluble Aβ oligomers.

It should be noted that the clinical diagnosis of probable AD in the NACC cohort and in AD clinical trials has so far been based on the 1984 NINCDS–ADRDA (pre-biomarker) set of criteria,[4] the specificity of which has been estimated at only ~70% in the NACC autopsy cohort. This is owing primarily to insufficient AD pathology, but also to the co-existence of contributing non-AD pathologies.[5] The percentage of incorrect diagnoses is very similar to the proportion of negative scans found in validation studies of amyloid PET radiotracers in patients with a clinical diagnosis of probable AD.

Monsell *et al.* noted that 33 of 37 *APOE*ε4* noncarriers and 12 of 13 *APOE*ε4* carriers with no or sparse neuritic plaques actually had a primary neuropathological diagnosis other than AD, the main alternative diagnoses being insufficient AD neuropathological change, cerebrovascular disease, hippocampal sclerosis, and Lewy body disease.[1] Most of the patients who had insufficient

neuropathological change to be diagnosed with AD could now be diagnosed with primary age-related tauopathy (PART), a new construct devised to classify patients with a predominantly amnestic syndrome, no or minimal cortical amyloid plaques, and a Braak stage of neurofibrillary degeneration usually between I and IV. However, whether PART is a different entity from AD or an AD variant is currently a matter of intense debate.[6,7] Small vessel ischaemic disease, hippocampal sclerosis, and cerebral amyloid angiopathy were shown to contribute to cognitive impairment independently of plaques and neurofibrillary tangles in a NACC autopsy cohort selected to represent the clinicopathological continuum of AD.[8] All of these conditions, as well as Lewy body disease and frontotemporal lobar degeneration, can mimic the clinical presentation of AD (Table 1).

To improve the specificity of the clinical diagnosis of Alzheimer dementia and its pre-dementia stages, new diagnostic criteria that incorporate biomarkers of brain amyloidosis (positive amyloid PET, decreased cerebrospinal fluid Aβ) and neurodegeneration (atrophy signature in brain MRI, increased cerebrospinal fluid tau and p-tau, decreased bilateral temporoparietal metabolism in ^{18}F-FDG–PET) have been developed.[9] However, a sizeable subset of individuals who are cognitively intact or have mild cognitive impairment (MCI) show at least one of the above neuronal injury markers characteristic of AD, but no PET-detectable amyloidosis. These individuals have been termed as having 'suspected non-Alzheimer pathophysiology' (SNAP). Longitudinal studies have revealed that MCI individuals with SNAP are at a high risk of being diagnosed with Alzheimer dementia at follow-up, estimated as 24% in 3 years in one recent study.[10] It is plausible that had these biomarkers been available, the individuals analysed by Monsell *et al.* at autopsy might have received a diagnosis of SNAP during their lifetime at an early stage of their dementing illness.

In conclusion, the study by Monsell *et al.* highlights the weakness of AD diagnosis based on purely clinical criteria, particularly among *APOE*ε4* noncarriers, and underscores the importance of biomarker-based diagnosis to dissect the pathological heterogeneity that often underlies dementia in elderly individuals. Future clinical trials of disease-modifying drugs will benefit from biomarker-based selection of patients.

Table 1 | Biomarkers for AD mimics

Condition mimicking AD	Pathological hallmarks	Biomarkers
Alzheimer dementia with 'insufficient' pathology for AD diagnosis	Low levels of amyloid plaques and neurofibrillary tangles	CSF Aβ and tau–p-tau* Amyloid PET* Tau PET: under evaluation*
PART and tangle-only dementia	Minimal or no amyloid plaques with Braak NFT stage I–VI (PART) or V–VI (tangle-only dementia)	CSF Aβ and tau–p-tau* Amyloid PET* Tau PET: under evaluation*
Cerebral amyloid angiopathy	Accumulation of Aβ in cortical and leptomeningeal capillaries and small arteries	CSF Aβ and tau–p-tau: intermediate levels between normal and AD Amyloid PET: normal<cerebral amyloid angiopathy<AD, increased occipital–global uptake ratio compared with AD
Lewy body disease	Widespread cortical α-synuclein-containing Lewy bodies and Lewy neurites	CSF α-synuclein: not validated DAT SPECT or ^{18}F-DOPA PET: reduced striatal uptake α-Synuclein PET radiotracers: under development
Cerebrovascular disease	Typically small vessel ischaemic disease	Regular brain MRI‡ is sensitive to white matter and basal ganglia small strokes, but not to cortical microinfarcts
Hippocampal sclerosis	Massive loss of pyramidal neurons in hippocampal CA1 and subiculum, with marked reactive gliosis that is not caused by NFTs or Lewy bodies. TDP-43-positive cytoplasmic neuronal inclusions or dystrophic neurites are often seen	Regular brain MRI‡ shows medial temporal lobe atrophy often indistinguishable from early AD
Frontotemporal lobar degeneration	Neurodegenerative diseases with marked atrophy of frontal and temporal lobes; classification based on the aggregated intracellular protein (tau, TDP-43 or FUS)	Low serum progranulin levels in patients with progranulin gene (*GRN*) mutation: under evaluation CSF biomarkers: not validated, under development PET radiotracers: tau under evaluation

*Levels of CSF biomarkers and uptake of PET markers can vary depending on the severity of the pathology. ‡Conventional 1.5 T brain MRI. Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease; CSF, cerebrospinal fluid; DAT, dopamine transporter; FUS, fused in sarcoma; NFT, neurofibrillary tangle; PART, primary age-related tauopathy; p-tau, hyperphosphorylated tau; SPECT, single-photon emission CT; TDP-43, TAR DNA-binding protein 43.

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Competing interests
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