alzheimer's research&therapy

COMMENTARY

Resistant to amyloid-β or just waiting for disease to happen?

Seth Love*

See related research by Moore *et al.*, http://alzres.com/content/4/3/18

Abstract

The post-mortem finding of abundant intracerebral accumulation of amyloid-β (Aβ) in the cerebral cortex of some people who develop minimal neurofibrillary pathology and remain cognitively intact until death (so-called pathological aging, or PA) challenges the orthodox view of the pathogenesis of Alzheimer's disease (AD). This issue of *Alzheimer's Research & Therapy* reports a study by Moore and colleagues, of the McKnight Brain Institute (Gainesville, FL, USA) and the Mayo Clinic College of Medicine (Jacksonville, FL, USA), who have performed the most detailed analysis to date of the levels and types of Aβ that accumulate in such cases. Although the levels of the different forms of Aβ in prefrontal cortex from patients with AD tended to be higher than those from patients with PA, the authors found extensive overlap between the two groups and suggest that PA is likely to represent a prodromal stage of AD. It is also possible that the quantity of Aβ is less important than the extent to which it accumulates intraneuronally or that some people are resistant to its effects – perhaps because of genetically determined differences in the inflammatory and astrocytic reactions to Aβ. The study emphasizes the continuing importance of careful human clinical and post-mortem studies in elucidating the pathogenesis of this disease.

The evidence that Alzheimer's disease (AD) results from excessive intracerebral accumulation of amyloid-β (Aβ), and of Aβ1-42 in particular, seems overwhelming. This is the most straightforward explanation for the development of AD in people with mutations in the amyloid-β precursor protein (APP) gene, duplication of the APP gene locus, or trisomy 21. This explanation fits in with the documented changes in the relative levels of the different forms of Aβ in patients with presenilin gene mutations and with the specificity of Aβ plaques to AD rather than any other disease (unlike aggregates of phospho-tau, which occur in a range of inflammatory, metabolic, and neurodegenerative diseases). Findings from *in vitro* and animal studies have been adduced to support the widely accepted thesis that excessive levels of particular forms and physical species of Aβ induce a series of deleterious metabolic processes that, over time, cause secondary damage to the brain, manifesting in the formation of neurofibrillary tangles and neuropil threads, dysfunction and degeneration of synapses, and, of course, impairment of cognition.

Why, then, should Aβ accumulate intracerebrally in large quantities in some people who do not develop neurofibrillary pathology to any significant extent and who remain cognitively intact until death? This phenomenon, sometimes termed pathological aging (PA), is a major challenge to our understanding of AD. Are the levels, forms, and physical species of Aβ that accumulate in PA truly comparable to those in AD, or are there other explanations for the apparent lack of adverse reaction to Aβ in some people? In this issue of *Alzheimer's Research & Therapy*, Moore and colleagues [1] address this question in a detailed post-mortem study of the profiles of Aβ in the prefrontal cortex in three approximately age-matched cohorts: 16 brains from patients with AD, eight from people with PA (characterized pathologically by the presence of numerous diffuse Aβ plaques but minimal neurofibrillary pathology), and seven from people with very little or no AD-type pathology. Although the levels of Aβ1-40, Aβ1-42, and N-terminally truncated Aβ were greatest in AD, there was extensive overlap with PA. This remained the case on further analysis of Aβ peptides by immunoprecipitation and mass spectrometry: a wider range of truncated fragments of Aβ was detected in tissue from some AD brains, but no consistent differences were identified between the AD and PA cohorts. The authors did find an intriguing disparity between the AD and PA cohorts in the proportion of cases with cerebral amyloid angiopathy (CAA) in which oxidized Aβ peptides could

*Correspondence: seth.love@bris.ac.uk
Dementia Research Group, Institute of Clinical Neurosciences School of Clinical Sciences, University of Bristol, Frenchay Hospital, Bristol, BS16 1LE, UK

BioMed Central © 2012 BioMed Central Ltd

be detected. Oxidized Aβ peptides were demonstrated in all 10 AD cases with CAA but in only one of six without CAA, raising the possibility that the presence of oxidized Aβ promotes the development of CAA (for example, by interfering with the perivascular drainage or endothelial uptake and transport of the peptide) or that CAA increases oxidative stress. In contrast, oxidized Aβ peptides were detected in as many of the PA cases that did have CAA as those that did not have it, although whether the severity of CAA was comparable in the AD and PA groups is not clear.

Other studies have also documented considerable overlap between the concentrations of soluble and insoluble forms of Aβ in AD and PA [2,3], but the paper by Moore and colleagues [1] presents the most exhaustive analytical comparison of the Aβ profile in these two groups. What, then, is the relevance of Aβ accumulation in the absence of significant neurofibrillary pathology? The present findings do not allow us to determine whether diffuse Aβ plaques represent a prodromal stage of AD or a benign form of Aβ accumulation: benign either because it is incidental to the neurofibrillary pathology (for example, if only intracellular Aβ is pathogenic) or because the people in whom it occurs are resistant to Aβ toxicity. Resistance could occur at the level of the neuron but could also reflect genetically determined differences in the inflammatory and astrocytic reaction to Aβ in AD and PA; data from genome-wide association studies indicate that the risk of developing AD is influenced by variation affecting several genes (*CLU*, *CR1*, and *MS4A6A*) that are involved in innate immunity [4-7].

Conclusions

Whatever the eventual explanation, the present findings emphasize, yet again, the critical importance of examining human patients and human brain tissue to test hypotheses derived from studying *in vitro* and animal models of neurodegenerative disease. The study by Moore and colleagues raises several questions. I expect most of the answers to come from further detailed assessment of patients and subsequent detailed post-mortem assessment of their brains.

Abbreviations

Aβ, amyloid-β; AD, Alzheimer's disease; APP, amyloid-β precursor protein; CAA, cerebral amyloid angiopathy; PA, pathological aging.

Competing interests

The author declares that he has no competing interests.

Published: 30 May 2012

References

1. Moore BD, Chakrabarty P, Levites Y, Kukar TL, Baine A-M, Moroni T, Ladd TB, Das P, Dickson DW, Golde TE: **Overlapping profiles of Aβ peptides in the Alzheimer's disease and pathological aging brains.** *Alzheimers Res Ther* 2012, **4:**18.
2. Maarouf CL, Daugs ID, Kokjohn TA, Walker DG, Hunter JM, Kruchowsky JC, Woltjer R, Kaye J, Castano EM, Sabbagh MN, Beach TG, Roher AE: **Alzheimer's disease and non-demented high pathology control nonagenarians: comparing and contrasting the biochemistry of cognitively successful aging.** *PLoS One* 2011, **6:**e27291.
3. Wang J, Dickson DW, Trojanowski JQ, Lee VM: **The levels of soluble versus insoluble brain Aβ distinguish Alzheimer's disease from normal and pathologic aging.** *Exp Neurol* 1999, **158:**328-337.
4. Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, Buros J, Gallins PJ, Buxbaum JD, Jarvik GP, Crane PK, Larson EB, Bird TD, Boeve BF, Graff-Radford NR, De Jager PL, Evans D, Schneider JA, Carrasquillo MM, Ertekin-Taner N, Younkin SG, Cruchaga C, Kauwe JS, Nowotny P, Kramer P, Hardy J, Huentelman MJ, Myers AJ, Barmada MM, Demirci FY, Baldwin CT, *et al.*: **Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease.** *Nat Genet* 2011, **43:**436-441.
5. Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrasquillo MM, Abraham R, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Jones N, Stretton A, Thomas C, Richards A, Ivanov D, Widdowson C, Chapman J, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Brown KS, Passmore PA, Craig D, *et al.*: **Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease.** *Nat Genet* 2011, **43:**429-435.
6. Jones L, Holmans PA, Hamshere ML, Harold D, Moskvina V, Ivanov D, Pocklington A, Abraham R, Hollingworth P, Sims R, Gerrish A, Pahwa JS, Jones N, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, *et al.*: **Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease.** *PLoS One* 2010, **5:**e13950.
7. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, *et al.*: **Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease.** *Nat Genet* 2009, **41:**1088-1093.

doi:10.1186/alzrt122
Cite this article as: Love S: Resistant to amyloid-β or just waiting for disease to happen? *Alzheimer's Research & Therapy* 2012, **4:**19.