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Commentary

Revisiting Alzheimer's Disease from a New Prospective: Can "Risk Factors" Play a Key Role?

J.L. Price[a], E.H. Rubin[b] and J.C. Morris[c*]

[a]*Department of Anatomy & Neurobiology and the Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, MO, USA*
[b]*Department of Psychiatry and the Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, MO, USA*
[c]*Departments of Neurology, Pathology and the Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, MO, USA*

A major theme of Drs Chen and Fernandez's article "Revisiting Alzheimer's Disease from a New Perspective: Can Risk Factors Play a Key Role?" is that sporadic Alzheimer's Disease (AD) may be the result of an accumulation of many "natural" age-related processes. The authors propose that these changes act additively to push aging cells over the brink: "It must be noted here that in very old cells, the life-supporting metabolisms are so much reduced, and intrinsic damages (plaques, tangles, free radicals, etc.) so much accumulated that the borderline between life and death has become very thin" (Section 4.1, 2nd paragraph). We agree that AD and age are strongly associated. However, we do not agree with Chen and Fernandez that there is evidence that age-related processes are causative of AD. For example, there is little if any scientific evidence to support their statement that a "sedentary lifestyle can cause AD", or that it might be possible to protect against AD by being "active in daily activities" (Section 4.2, 3rd paragraph).

One emphasis of Washington University's Alzheimer's Disease Research Center has been to develop clinical methods to distinguish healthy aging from the earliest clinically detectable stage of AD, and then to compare neuropathologic changes in these two groups of cases. These studies, together with reports from other groups, help us better understand the relationships between aging and Alzheimer's disease.

These studies document that the formation of tangles and other neurofibrillary changes are age-related. Tangles are found in virtually all individuals beyond a certain age (1,4). There is slight disagreement about when this occurs (between about 50 and 70 years of age), but there is growing consensus that tangles eventually become ubiquitous. In all cases, tangles occur preferentially in vulnerable neurons (initially pyramidal cells of the entorhinal and perirhinal cortices and field CA1 of the hippocampus) and the same pattern of preferential vulnerability continues through the progression of AD. In non-demented cases the density of tangles increases exponentially with increasing age, although at ages below about 90–95 the number of tangles remains relatively low (4). Because of this, it appears that the formation of tangles in nondemented aging is a relatively mild process, although tangles are clearly pathological, and closely related to the

* Corresponding author: J.C. Morris, Department of Neurology, Campus Box 8111, Washington University School of Medicine, 660 S. Euclid Avenue, St. Louis, MO 63110, USA, Tel.: +1 314 286 1967, Fax: +1 314 286 2448, E-mail: morrisj@neuro.wustl.edu

cell death that begins in very mild AD (Clinical Dementia Rating or CDR 0.5; (2)). It is likely that age-related tangle formation would not cause a serious health problem within current life spans. This is consistent with the observations that in the absence of disease there is little evidence for cognitive decline with age (5).

The incidence of amyloid plaques also appears to increase with age (1), although their relation to age is very different than that of tangles. In particular, some aged individuals do not have plaques, even into their nineties (1,4). Furthermore, the density of total plaques does not increase markedly with age or severity of AD dementia, although there is an increase in the number of neuritic plaques (4). On the other hand, plaques appear to be a much better marker for the onset of AD than tangles (3).

Amyloid-β plaques also seem to be the primary target of risk factors, including apolipoprotein E genotype and all of the AD-related genetic factors identified so far (6), so it appears that the impact of risk factors is mainly related to plaques. Since plaques correspond well to the onset of the disease, their variable incidence can explain the fact that some people get AD and others do not (at least within current life spans). We have argued that the presence of large amounts of amyloid-β, either in plaques or in a diffusable form, is the factor that converts the relatively mild tangle formation seen in aging into the rapid neurofibrillary change and associated catastrophic neuronal dysfunction and death that underlie the dementia of AD (4).

Although studies of human aging can be difficult to interpret, it is important to distinguish myth from fact. Chen and Fernandez rightfully implicate some age-related processes in the development of AD, but go beyond current evidence in claiming that age alone may be responsible for AD. Our data show that it is possible to live into the tenth decade (perhaps beyond) without clinical or pathological AD, suggesting that AD may not be inevitable. Much more study will be needed, of course, before the complex relationship between aging and AD is fully understood.

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