

Synaptic loss and pathological change in older adults—aging versus disease?

Joseph L. Price, Ph.D.^a, Daniel W. McKeel, Jr., M.D.^b, John C. Morris, M.D.^{b,c,*}

*Departments of ^aAnatomy and Neurobiology
^bPathology*

^cNeurology, and the Alzheimer's Disease Research Center, Washington University, St. Louis, Missouri

Accepted 25 October 2000

In their short paper in this issue, “Life span and synapses: Will there be a primary senile dementia?”, Terry and Katzman argue the interesting hypothesis that Alzheimer’s disease (AD) occurs against a background of neuropathologic change that occurs with age. (A similar hypothesis could be raised for many age-associated disorders, including Parkinson’s disease, arteriosclerosis, and arthritis). They focus on the density of neocortical synapses, because synaptic loss is relevant to cognitive impairment and because they previously noted a decrement in presynaptic terminals beginning at age 20 years [9]. If synapses are lost with age at the rate suggested by Terry and Katzman, the age at which sufficient synaptic loss occurs to produce dementia is estimated to be about 130 years. Additional pathology associated with AD or other disorders, in combination with underlying age-related synaptic loss, would result in dementia at an earlier age.

Are there data from analogous neuropathologic markers to support this hypothesis? We previously reported that neurofibrillary tangle formation in vulnerable areas such as entorhinal cortex has a similar relationship to age. That is, tangles occur in virtually all individuals age 50 and older and the density of tangles increases with age even in the absence of dementia [12]. The distribution of neurofibrillary tangle formation with age qualitatively is very similar to the quantitatively greater neurofibrillary change associated with AD. We have argued that AD occurs when β -amyloid plaques accumulate to a sufficient degree to exacerbate the age-related tangle formation [10,12]. Although the development of any tangle almost certainly is pathological (e.g., the laminar and areal pattern of tangle formation in the area

such as the entorhinal cortex correlates closely with the pattern of neuron loss in AD), the number of tangles that form with age alone is relatively low. Without the accelerating effect of β -amyloid plaques, therefore, age-related tangle formation produces relatively little cognitive deficit, at least in current life spans. It may be that age-related synaptic loss similarly may occur but would not produce dementia unless exacerbated by disorders such as AD. If it becomes common for individuals to live beyond 100 years, however, age-related neurofibrillary change and synaptic loss may accumulate to clinically important levels and cause dementia even in the absence of disease. The relevance of this hypothesis may be significant if disease-related pathologic change is prevented, as may occur with anti-amyloid strategies.

The data showing synaptic loss with age may be challenged, however. Not all investigators agree that there is synaptic loss throughout the life span [2,7]. Stereologic studies indicate that in the absence of disease there is little or no neuronal loss with age in most cortical regions [4,5,14]. It also has been difficult to objectively to confirm cognitive decline other than reduced physical and cognitive reaction speed in nondemented individuals [13]. These findings suggest that healthy brain aging may be possible if AD or other neurodegenerative disease somehow can be avoided. They also raise the issue of whether the cases used for the synaptic counts in the Terry and Katzman studies represented a truly healthy sample or whether the observed synaptic loss was an effect of contamination by cases in the very early stage of AD.

We studied 69 autopsied individuals over the age of 90 and found that neuropathologic Alzheimer’s disease was very common [6]. Only 6 cases did not meet pathologic criteria for AD and even these individuals had some plaques and tangles. Thus, the risk of contamination by unsuspected AD in putatively normal samples of very old individuals is high. The 25 cases used to obtain the synaptic density data

* Corresponding author. Tel.: +(314) 286-2881; fax: +(314) 286-2763.

E-mail address: morrisj@neuro.wustl.edu (J.C. Morris).

Supported by National Institute on Aging grants AG 03991 and AG 05681.

reviewed in Terry and Katzman's paper were selected to be "without any apparent neurologic, cognitive, or neuropathic abnormality" [9]. However, these cases apparently were not assessed with methods sensitive to very mild cognitive impairment. Because very mildly demented cases have been shown to have substantial neuropathologic burden [11], including neurofibrillary tangles, β -amyloid plaques, and cell loss in vulnerable areas, inclusion of even a few of such cases in the sample studied by Terry and Katzman would skew the results so that disease-related synaptic loss could be interpreted as age-related. Nine of the 25 cases used for the synaptic counts (mostly older cases) in the Terry and Katzman study were reported to have plaques.

The authors' assertion that synaptic density is a more relevant marker for dementia than plaques and tangles also can be challenged [3]. Our data [1] showed a moderate correlation between plaque density and dementia severity as measured by the Clinical Dementia Rating (CDR) in the same three cortical regions used to count synapses in the Terry and Katzman data. Also, the use of thioflavin S to quantify plaques in only three fields in each area may result in an underestimation of plaque density [8,15]. Several studies from our Center have documented that truly nondemented aging is best distinguished from very early stage AD by the total plaque burden seen in AD, which includes diffuse plaques [1,11,12]. These data appear to establish that even diffuse plaques have importance in relation to the pathogenesis of Alzheimer-type dementia in the old and very old.

In summary, the hypothesis put forth by Terry and Katzman that aging effects may eventually produce dementia even in the absence of disease is important and deserves wide discussion. Other age-related factors, such as neurofibrillary change, also may have similar implications and may interact with synaptic loss. The specific observations on synaptic loss with age need to be confirmed to ensure that the data are valid and that the subject population is not contaminated with very mild AD. Further, the relationship of synaptic loss to amyloid plaque density needs to be examined with more sophisticated models of the disease process that recognizes the strong correlation of plaque density with the onset of AD.

References

- [1] Berg L, McKeel DW Jr, Miller JP, Storandt M, Rubin EH, Morris JC, Batty J, Coats M, Norton J, Goate AM, Price JL, Gearing M, Mirra SS, Saunders AM. Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease: Relation of histologic markers to dementia severity, age, sex, and ApoE genotype. *Arch Neurol* 1998;55:326–35.
- [2] Brown DF, Risser RC, Bigio EH, Tripp P, Stiegler A, Welch E, Eagan KP, Hladik CL, White CL III. Neocortical synapse density and Braak stage in the Lewy body variant of Alzheimer disease: a comparison with classic Alzheimer disease and normal aging. *J Neuropathol Exp Neurol* 1998;57:955–60.
- [3] Dickson DW, Crystal HA, Bevona C, Honer W, Vincent I, Davies P. Correlations of synaptic and pathological markers with cognition of the elderly. *Neurobiol Aging* 1995;16:285–98.
- [4] Gomez-Isla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, Parisi JE, Hyman BT. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann Neurol* 1997;41:17–24.
- [5] Gomez-Isla T, Price JL, McKeel DW Jr, Morris JC, Growdon JH, Hyman BT. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. *J Neurosci* 1996;16:4491–500.
- [6] Morris JC, Hurst E, McKeel DW, Price JL, Rubin E, Grant EA, Berg L. Healthy Brain Aging in Nonagenarians and Centurians. *Neurol Aging Abstracts from the 7th Int'l Con. on AD 2000*; 21:S280–1.
- [7] Huttenlocher PR. Synaptic density in human frontal cortex—developmental changes and effects of aging. *Brain Res* 1979;163:195–205.
- [8] Lamy C, Duyckaerts C, Delaere P, Payan CH, Fermanian J, Poulain V, Hauw J-J. Comparison of seven staining methods for senile plaques and neurofibrillary tangles in a prospective series of 15 elderly patients. *Neurobiol Appl Neurobiol* 1989;15:563–78.
- [9] Masliah E, Mallory M, Hansen LA, DeTeresa R, Terry RD. Quantitative synaptic alterations in the human neocortex during normal aging. *Neurol* 1993;43:192–7.
- [10] Morris JC. Is Alzheimer's disease inevitable with age? *J Clin Invest* 1999;104:1171–3.
- [11] Morris JC, Storandt M, McKeel DW Jr, Rubin EH, Price JL, Grant EA, Berg L. Cerebral amyloid deposition and diffuse plaques in "normal" aging: Evidence for presymptomatic and very mild Alzheimer's disease. *Neurology* 1996;46:707–19.
- [12] Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann Neurol* 1999;45:358–68.
- [13] Rubin EH, Storandt M, Kinschler DA, Grant EA, Morris JC, Berg L. A prospective study of cognitive function and onset of dementia in cognitively healthy elders. *Arch Neurol* 1998;55:395–401.
- [14] West MJ. Regionally specific loss of neurons in the aging human hippocampus. *Neurobiol Aging* 1993;14:287–93.
- [15] Wisniewski H, Wen G, Kim K. Comparison of four staining methods on the detection of neuritic plaques. *Acta Neuropathol (Berlin)* 1989; 78:22–7.