Open peer commentary

Life span and synapses: will there be a primary senile dementia?

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Received 15 August 2000; accepted 24 August 2000

Abstract

In the course of normal aging from about age 20 to 100, the population density of neocortical synapses declines toward, but not reaching, the level found in Alzheimer disease. A deficiency of synapses at birth or due to inadequate childhood education would theoretically cause the synaptic slope to reach the Alzheimer level early. The normal slope would cross into that dementia range at about age 130, resulting in true primary senile dementia without regard to the presence of plaques and tangles. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Synapse number; Life span; Aging; Deficiency; Birth; Illiteracy; Primary dementia

It is widely accepted that the cognitive changes in Alzheimer disease are directly related to the loss of cerebral connectivity [1]. Symptomatic dementia occurs when there is about 40% loss of neocortical synapses as compared with normal adults [2], and it is that decrement which creates the disconnections. Utilizing synaptophysin antibody to quantify presynaptic terminals, we demonstrated [3] several years ago that in the course of normal aging there is a steady decline in the concentration of neocortical synapses, beginning at least at the age of about twenty years (Fig. 1). Questions, however, might well arise concerning both ends of that continuum.

For example, what would be the hypothetical long term result of a handicap present at birth such that fewer synapses develop? Down’s syndrome would be an example [4]. Here the synapse concentration is low in infancy and would probably fall as a function of age, at best, at a normal rate; that is, parallel to the line in Fig. 1. That decline would bring the synaptic density at an early age (Fig. 2) to the 60% (of normal) threshold established in Alzheimer disease [2], and dementia would be the result because of the loss of intracerebral connectivity. This synaptic loss probably has a greater effect than plaques and tangles.

The findings concerning the increased prevalence of dementia and Alzheimer disease in the illiterate elderly population [5] might be similarly explained. One can presume from data on experimental animals [6] that education brings about multiplication of cortical synapses and increases their plasticity. A lesser rise in synaptic density would occur with deficient education, and again the age-related synaptic decline would bring the deprived patient to the critical dementia threshold earlier than otherwise (Fig. 3).

Current population projections predict that there will be about a million centenarians in the United States by the middle of this century [7]. Now, what if more people, living
past 100, begin to approach the current assumed life span of 120, or even 140 if life span increases as suggested by some? We can extend the declining synaptic line of figure one beyond the original plot on the abscissa and show that the average patient would cross the critical 60% threshold at about 130 years, and would be demented on that basis; that is in the absence of plaques and tangles or other evidence of Alzheimer Disease (Fig. 4). This would be true primary senile dementia, and would affect half the “normal” (non Alzheimer) survivors. Life extension without protecting our cortical synapses would be a disastrous error in sociologic terms.

Admittedly, these situations of synaptic shortage in birth abnormality and limited education, and synaptic loss with extended life span are all hypothetical since measurements of synapse concentration have not been done as a function of age in each of these conditions. Nevertheless, the implications of the available data are very clear, and these hypotheses will become testable.

References