THINKING OUTSIDE THE BOX IN ALZHEIMER DISEASE TREATMENT

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1 INTRODUCTION

Alzheimer disease (AD) is the most prevalent neurodegenerative disease worldwide and affects over 4 million Americans [1]. As the average life expectancy increases in the United States and throughout the world, so does the number of elderly men and women who become increasingly susceptible to AD as they age. In fact, it is estimated that by 2050, 14 million Americans will have AD if preventative treatments do not become available [2]. The cost of treatment is considerable: National direct and indirect cost of caring for AD patients have been estimated to be upward of $100 billion per year, a figure that will rise as the prevalence increases [3].

AD is characterized by two basic neuropathological lesions, the senile plaque and the neurofibrillary tangle. The major protein component of the senile plaque is amyloid-β (Aβ), while the major protein component of the neurofibrillary tangle is hyperphosphorylated tau [1]. It is important to point out, however, that our understanding of the neuropathology of AD is based upon autopsy examination of end-stage disease. Thus, plaques and tangles are not "diagnostic" of AD; indeed, they may be seen in variable, and often large, numbers in cognitively intact elderly individuals. Rather, they are quantitative phenomena, being relatively more numerous in AD compared to controls. Application of standard criteria, therefore, yields a spectrum of diagnostic certainty in the case of Consortium to Establish a Registry for Alzheimer's Disease (CERAD) or National Institute on Aging (NIA)-Reagan criteria [4, 5], or a spectrum of stages in the case of Braak criteria [6]. It is also interesting to note that among the various neurodegenerative diseases, the one with the greatest overlap with "normal" aging, and the one with the most diagnostic uncertainty, is AD. Degenerative tauopathies such as corticobasal degeneration and progressive supranuclear palsy, for example, are essentially impossible to confuse with normal aging pathologically; this is also the case for synucleinopathies such as multiple system atrophy. Even Lewy body dementia, while nosologically cumbersome, is much more qualitative than classic AD. While Lewy bodies are described as age-related lesions, they are uncommonly seen in aged brains (i.e., are more "pathological"), whereas neurofibrillary tangles are essentially invariable in the medial temporal lobe of the elderly, as are amyloid deposits in the cerebral cortex.

In short, the diagnosis of AD on the basis of plaques and tangles at autopsy overlaps substantially with normal aging, and it follows that accumulation of plaques and tangles is as much an age-related process

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