Update on Alzheimer's and the Dementias: Introduction

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KEYWORDS

• Alzheimer's disease • Dementia • Amyloid cascade hypothesis • Prevention • Intervention • Genetic • Presymptomatic • Diagnostic criteria

KEY POINTS

- Incipient neuropathologic changes of Alzheimer's disease (AD) precede overt clinical signs by 15 to 20 years.
- It is becoming more evident that AD is not a single entity but rather a group of diseases at least partially differentiable by their underlying genetic architecture.
- There may be pathophysiological subtypes of AD depending on the age of disease onset.
- In light of the recognition of the long presymptomatic course of AD and its recalcitrant nature once established, there is increasing focus on its prevention.

With the growing population and overall extension of life expectancy in many parts of the world, the prevalence of dementia is becoming alarmingly high. By the middle of this century, the numbers of persons in the United States with Alzheimer's disease (AD), the most common cause of dementia, are expected to reach 13.8 million.[1] Although some studies in industrialized countries suggest a decrease in dementia incidence in recent years, possibly as the result of better control of risk factors for vascular disease,[2] the worldwide prevalence numbers are sure to continue to increase.[3] It is hopeful that better control of modifiable risk factors (eg, hypertension and hypercholesterolemia) might help to stem the epidemic,[4] but the constant influences of population growth, genetics, and aging ensure an increasing need for resources to care for affected individuals.

The characteristic neuropathology of AD (amyloid plaques [APs] and neurofibrillary tangles [NFTs]) contribute to the cause of dementia in approximately two-thirds of dementia cases and the effect of risk factor control on this pathology is less certain. Observational and interventional studies attempting to directly address these specific pathologic changes had previously been hampered by our inability to definitively

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identify them in living persons. However, over the last 15 years we have developed biochemical (eg, levels of Aβ42, tau, and p-tau in the cerebrospinal fluid) and imaging (eg, amyloid and tau PET) modalities that permit us to positively identify AD pathology during life, allowing for an augmented understanding of AD biology and its response to treatment. It is now clear that AD neuropathologic changes can precede overt clinical symptoms by 15 to 20 years, opening up the window for secondary prevention opportunities and the reconceptualization of AD from a "clinicopathologic" entity to a condition defined principally by biomarker changes. In 2011, in a joint venture between the National Institute on Aging and the Alzheimer's Association, criteria for "dementia due to AD,[5]" "mild cognitive impairment due to AD,[6]" and "preclinical AD pathology,[7]" based on the presence or absence of AD-specific and nonspecific biomarker changes were put forth. Consideration is now being given to revising these criteria further to define AD based purely on the presence of AD-specific biomarkers, at least for research purposes.

The APs and NFTs that are the "hallmarks" of AD and have been the focus of a multitude of studies into the etiologic mechanisms of the disease; however, there remains substantial uncertainty regarding what "upstream" and "downstream" events are most relevant and should be addressed with therapeutic interventions. Fueled by the discovery that the genetic mutations that cause young-onset Mendelian forms of AD (autosomal-dominant AD) lead to aberrant cleavage of amyloid precursor protein, fragments of which largely comprise the APs and cerebral amyloid angiopathy that characterize the illness, the "amyloid cascade hypothesis" was elaborated and has since dominated the field.[8] This posits that the misprocessing of amyloid precursor protein (APP) is central to causing all forms of AD, with non-Mendelian AD typically of later onset potentially being due to a decreased ability of the body to eliminate APP derivatives (eg, by inefficient transport of Aβ by apolipoprotein E variants associated with an increased risk of AD[9]). Interventions directly targeting the amyloid cascade have been demonstrated to positively affect Aβ production and deposition,[10] but have not yet shown substantive clinical efficacy.[11] Although still of substantial heuristic value, additional mechanisms occurring before, in association with, or consequent to amyloid deposition must be a growing focus of AD research. Recent, large-scale, genome-wide association studies in dementia have enabled the identification of many genetic variants, each with a relatively small influence on the ultimate risk of developing AD[12] (http://www.alzgene.org). Variants in genes with roles in inflammation, endocytosis, protein trafficking, and lipid transport have all been implicated. The degree to which any individual variant contributes to the development of a given case of "sporadic" AD certainly differs across cases, highlighting the importance of consideration of AD as the "Alzheimer's diseases" rather than as a monolithic entity.

After Alois Alzheimer's original description of AD in 1907, AD was thought of for decades as "presenile dementia," defined as when the clinicopathologic entity occurs before age 65. Cases of dementia occurring after that age, in the "senile" period, were attributed to "hardening of the arteries" or as the inevitable consequences of normal aging. In the late 20th century, the recognition of a continuum in the neuropathology between the majority of dementia cases across these ages led to a unification of the disease into a single entity.[13,14] However, in more recent years, with the help of more sophisticated genetic, imaging, and other tools, important differences between AD of young and late onset have come to light. Young-onset AD is more likely to have a nonamnestic presentation (eg, with logopenia, visuospatial deficits, or apraxia), have different atrophy patterns, and likely different genetic origins. Although the *APOE* ε4 variant, particularly when present in the homozygous state, decreases the age of AD onset, it is less frequently present in those with atypical presentations. That the