MAYO CLINIC

Alzheimer Disease: Scientific Breakthroughs and Translational Challenges

Richard J. Caselli, MD; Thomas G. Beach, MD, PhD; David S. Knopman, MD; and Neill R. Graff-Radford, MD

From the Department of Neurology, Mayo Clinic, Scottsdale, AZ (R.J.C.); Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, AZ (T.G.B.); Department of Neurology, Mayo Clinic, Rochester, MN (D.S.K.); and Department of Neurology, Mayo Clinic, Jacksonville, FL (N.R.G.-R.).

CME Activity

Target Audience: The target audience for *Mayo Clinic Proceedings* is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine and who wish to stay abreast of advances in medical research.

Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

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Learning Objectives: On completion of this article, you should able to (1) recognize the basis for the amyloid hypothesis about the pathogenesis of Alzheimer disease and current approaches to disease-modifying therapy; (2) differentiate the effect of multiple genetic risk factors identified in genome-wide screening analyses with the major autosomal dominant forms as well as apolipoprotein E ε4; (3) correlate imaging biomarkers with the neuropathology of Alzheimer disease; and (4) recognize the extended preclinical course of Alzheimer disease, its neuropathological basis, and its expression in the form of biomarkers.

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Abstract

Alzheimer disease (AD) was originally conceived as a rare disease that caused presenile dementia but has come to be understood as the most prevalent cause of dementia at any age worldwide. It has an extended preclinical phase characterized by sequential changes in imaging and cerebrospinal fluid biomarkers with subtle memory decline beginning more than a decade before the emergence of symptomatic memory loss heralding the beginning of the mild cognitive impairment stage. The apolipoprotein E ε4 allele is a prevalent and potent risk factor for AD that has facilitated research into its preclinical phase. Cerebral Aβ levels build from preclinical through early dementia stages followed by hyperphosphorylated tau–related pathology, the latter driving cognitive deficits and dementia severity. Structural and molecular imaging can now recapitulate the neuropathology of AD antemortem. Autosomal dominant forms of early-onset

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familial AD gave rise to the amyloid hypothesis of AD, which, in turn, has led to therapeutic trials of immunotherapy designed to clear cerebral amyloid, but to date results have been disappointing. Genome-wide association studies have identified multiple additional risk factors, but to date none have yielded an effective alternate therapeutic target. Current and future trials aimed at presymptomatic individuals either harboring cerebral amyloid or at genetically high risk offer the hope that earlier intervention might yet succeed where trials in patients with established dementia have failed. A major looming challenge will be that of expensive, incompletely effective disease-modifying therapy: who and when to treat, and how to pay for it.

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Much has changed since November 3, 1906, the day Alois Alzheimer first presented the unusual case of Auguste Deter to the Society of Southwest German Psychiatrists. Her symptoms of delusional jealousy, paranoia, and memory loss began insidiously at the age of 51, ended with her death at age 55, and led to the original conception of Alzheimer disease (AD) as a rare cause of presenile dementia.[1] The first major change occurred 70 years later when Katzman[2] and Terry[3] argued that the disease bearing Alzheimer's name was also the cause of senile dementia in the elderly, a much more prevalent condition, and so far from previous conceptions AD came to be understood as highly prevalent, the major cause of dementia at any age, and a major cause of death. A second and more recent major change has been to dispel the notion that AD can only be confirmed at autopsy. Advances in brain imaging have made antemortem confirmation a reality (within the research arena). Genomics and many more advances have further led to our current concept of AD and constitute the bulk of this review.

CLINICAL BACKGROUND

When symptoms first become apparent, patients are forgetful but still functioning independently. The diagnostic term *mild cognitive impairment* (MCI) was originally introduced to define a nondisabling but progressive monosymptomatic amnestic syndrome[4-6] and evolved into a broader classification of early, nondisabling cognitive deficits.[7,8] Longitudinal studies[4,5,9,10] of patients with MCI have shown that approximately 10% to 15% of patients per year lose their ability to function reasonably independently, the defining characteristic of dementia. After 5 years, about half of all patients with MCI will meet criteria for dementia, particularly AD, and after 10 years, most will have AD or another dementia syndrome. At autopsy, 70% to 80% of patients who originally received a diagnosis of MCI prove to have AD as the major component of the dementia.[10,11]

The latest version of the National Institute on Aging Alzheimer's Disease Center's Uniform Data Set characterizes AD dementia as an "amnestic multidomain dementia syndrome,"[12] meaning progressive memory loss over months to years with the gradual emergence of executive, language, visuospatial, and other deficits with or without behavioral features such as sundowning and paranoia. Diagnostic criteria are summarized in Table 1.[13] Alzheimer *disease* does not always follow the canonical neuropathological pattern, however. Variant syndromes reflect a different pathological topography. Visual variant AD or posterior cortical atrophy reflects progressive visual impairment related to early degenerative involvement of visual cortices.[14] Other focal variants of AD affect language, motor, and executive functions.[15-18]

NEUROPATHOLOGY

Neuropathologically, AD is characterized by 2 hallmark features: amyloid plaques and neurofibrillary tangles (NFTs) (Figure 1). Morphologically, amyloid plaques are described as either diffuse or neuritic. Both types may be seen in individuals without dementia, in whom they may indicate an increased risk of progression to dementia. Neuritic plaque is associated with cognitive impairment, whereas for diffuse plaques this relationship is tenuous. The primary event in plaque formation is the deposition of insoluble Aβ amyloid, whereas the "neuritic" elements