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# Update on Alzheimer's and the Dementias: Introduction

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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 U.S. with Alzheimer's disease (AD), the most common cause of dementia, are expected to reach 13.8 million[1]. Though 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], worldwide prevalence numbers are still sure to continue to increase[3]. It is hopeful that better control of modifiable risk factors (e.g. hypertension and hypercholesterolemia) might help might help to stem the epidemic[4] but the constant influences of population growth, genetics, and aging assure an increasing need for resources to care for affected individuals.

The characteristic neuropathology of AD (amyloid plaques, or 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 pathological changes had previously been hampered by our inability to definitively identify them in living persons. However, over the last 15 years we have developed biochemical (e.g. levels of Aβ42, tau, and p-tau in the cerebrospinal fluid) and imaging (e.g. amyloid and tau positron emission tomography, or PET) modalities that permit us to definitively identify AD pathology during life, allowing for an augmented understanding of AD biology and its response to treatment. It is now clear that identifiable AD neuropathological changes can precede overt clinical symptoms by 15 to 20 years, opening up the window for secondary prevention opportunities and the re-conceptualization of AD from a "clinicopathological" 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],"

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"mild cognitive impairment due to AD[6]," and "preclinical AD pathology[7]," based on the presence or absence of AD-specific and non-specific biomarker changes were put forth. Consideration is now being given to revising these criteria still 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 have been the focus of a multitude of studies into the etiological mechanisms of the disease but there is still 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 or ADAD) lead to aberrant cleavage of amyloid precursor protein, fragments of which largely comprise the APs and cerebral amyloid angiopathy (CAA) that characterize the illness, the "amyloid cascade hypothesis" was elaborated and has since dominated the field[8]. This posits that mis-processing of 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 (e.g. 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]. Though still of substantial heuristic value, additional mechanisms occurring prior to, 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 clinicopathological entity occurs prior to 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 20$^{th}$ 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 non-amnestic presentation (e.g. with logopenia, visuospatial deficits, or apraxia), have different atrophy patterns, and likely different genetic origins. Though 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 *APOE* ε4 variant is clearly overrepresented in typical AD of onset in the 70's but less so in this atypical young-onset group and in the extreme elderly when multiple diverse neuropathologies are commonly found, attests to the genetic heterogeneity of the disorder that may ultimately be reflected in differential response to treatment. Though the degree to which AD of young and late onset is similar and distinct is

not yet comprehensively defined, age at onset does appear to be an important factor to consider when studying AD pathogenesis and response to treatment.

With increasing longevity, more neuropathological studies, and the advent of more sophisticated diagnostic modalities, there was a shift from the concept of senile dementia having a purely vascular etiology ("hardening of the arteries") to a neurodegenerative disease associated with APs and NFTs[15]. Both large and small cerebral infarcts as well as diffuse cerebral ischemia can contribute to cognitive impairment and dementia though pure "vascular dementia" is relatively rare in neuropathological studies as concurrent AD pathology is often present. Nonetheless, as AD and cerebrovascular disease share many risk factors, and in light of a growing appreciation of the relevance of CAA and recent animal studies suggesting how these pathologies might act in a synergistic way, there is increasing focus on dysfunction of the "neurovascular unit" as inducing or propagating AD pathology[16]. Though it remains to be defined to what degree this is the case, this approach could potentially identify targets amenable to intervention.

As indicated above, clinical trials of putative disease-modifying treatments have so far been disappointing, despite at least some evidence of target engagement. Most such studies have been initiated well into the symptomatic stage of the disease, when APs and NFTs are well established and substantial neuronal and synapse loss has already occurred. It may be that these interventions have been "too little, too late." Our current understanding of the genetic nature of AD and our ability to measure AD pathology during the extended presymptomatic stage has provided the opportunity for secondary prevention studies. Specifically, there are currently studies ongoing in asymptomatic elderly persons with positive amyloid PET scans[17], carrying dominantly inherited AD mutations[18, 19], and homozygous for the *APOE* ε4 genotype[19]. However, it remains to be seen if these approaches will be effective and it may be necessary to ultimately perform primary prevention studies in which the intervention occurs prior to any discernible AD pathology. Until effective disease-modifying therapies are identified, we must remain agnostic and unprejudiced in our quest to identify targets and implement intervention strategies for AD.

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## Key Points

Though the numbers of dementia cases are rising worldwide, there is evidence that incidence rates appear to be decreasing, at least in industrialized countries.

Incipient neuropathological changes of Alzheimer's disease precede overt clinical signs by 15 to 20 years. We now have biochemical and imaging markers that enable us to identify these early changes and allow us to better differentiate AD from other causes of dementia.

The amyloid cascade hypothesis is the prevailing theory for the etiology of AD and has led to the development of many putative disease-modifying interventions. Thus far, however, these have not been demonstrated to be substantively effective and additional and diverse approaches need to be considered.

With the initial identification of rare Mendelian forms of AD and now multiple genetic variants conferring differential risk for AD, it is becoming more evident that AD is not a single entity but rather represents a group of diseases at least partially differentiable by their underlying genetic architecture.

Since AD was first described, there has been a shift from the idea that AD occurring during the presenium was an entity distinct from late-onset AD, to their consideration as a single entity, and now back to the recognition that AD occurring at different ages may represent pathophysiological subtypes of the disease.

Though the conceptualization of dementia occurring during senility simply as "hardening of the arteries" is largely discounted, there is a growing understanding of the contributions of cerebrovascular disease into cognitive impairment in the elderly and potentially in the causation of AD.

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.