Published in final edited form as:

Mt Sinai J Med. 2010 ; 77(1): 1–2. doi:10.1002/msj.20166.

Alzheimer's Disease: New Light on Etiology and Management

**Nikolaos K. Robakis, PhD [A.P. Slaner Professor for Alzheimer's Disease Research]
[Professor of Neurobiology]**

Center for Molecular Biology and Genetics of Neurodegeneration, Mount Sinai School of Medicine, New York, NY

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the central nervous system leading to the most common form of age-associated dementia. More than a century has passed since 1907 when Alois Alzheimer first described the neuropathological hallmarks of the dementia that now bears his name. During this time, our understanding of the biological, environmental, and genetic factors that drive this disorder followed progress in the fields of molecular biology, neuroscience, and genetics. It could be said that the modern era of understanding the biological factors involved in AD started in the early 1980s with the first efforts to elucidate the molecular nature of the neuropathological markers found in the brains of affected individuals. These markers include neuritic amyloid plaques, neurofibrillary tangles, and cerebrovascular amyloidosis. Interestingly, a volume on a symposium on amyloid and amyloidosis held in 1979 makes no reference to the amyloidosis of AD,¹ and this indicates that even at this late date, there was little effort directed at the neuropathology of AD. Neuritic amyloid plaques are complex extracellular structures containing at their core amyloid deposits of fibrillar amyloid beta (A β) protein surrounded by reactive astrocytes, microglia, and dystrophic neurites. In contrast to the extracellular localization of neuritic amyloid plaques, neurofibrillary tangles accumulate inside neuronal cells and consist mainly of paired helical filaments of hyperphosphorylated tau protein. Many patients also display high levels of amyloid deposits of A β peptides in brain blood vessels; this condition is termed *cerebrovascular amyloidosis*. It is now believed, however, that dementia is caused by extensive neuronal and synapse losses in the hippocampus and neocortical regions of the brain.

AD is a serious health problem: it is estimated that by 2020, 30 million people will be afflicted worldwide. In the United States of America, the average cost of care per patient from diagnosis to death has been estimated to be as high as \$174,000. The first clinical symptoms of AD include a loss of recent memory, faulty judgment, personality changes, and a progressive loss of reasoning power. At later stages, patients become agitated, aggressive, and delusional with sleep disturbances and loss of reasoning. Most AD cases occur after the ages of 65 or 70, and death ensues about 10 to 15 years after the appearance of the first symptoms. The vast majority of AD cases are termed *sporadic* because they lack a clear

Address Correspondence to: Nikolaos K. Robakis, Center for Molecular Biology, and Genetics of, Neurodegeneration, Mount Sinai School of Medicine, New York, NY, nikos.robakis@exchange.mssm.edu.

DISCLOSURES

Potential conflict of interest: Nothing to report.

genetic etiology, but about 5% of all cases display clear genetic linkages and are classified as familial Alzheimer's disease (FAD). These usually occur at younger ages and follow a more aggressive clinical course than the sporadic forms of AD. The brain neuropathology, however, is similar in sporadic AD and FAD, and this suggests the involvement of common cellular mechanisms in all AD cases. Despite intense efforts, there is still no chemical test to assay for AD, and because clinical symptoms similar to those of AD may be caused by a number of conditions or diseases, including vascular dementia, a definite diagnosis of AD is possible only after clinical symptoms are combined with a postmortem examination of brain tissue for the detection of plaques and tangles. In this volume, Daniel Perl gives a comprehensive review of the neuropathological and clinical findings that characterize AD.

Although in the last quarter of a century we have learned a great deal about this disease, including the chemical composition of the neuropathological markers of AD and information about the genetics of this disorder, the main mechanisms responsible for the accelerated neuronal cell loss that results in dementia are still poorly understood. It is generally accepted, however, that like the pathogenesis of many other disorders, the pathogenesis of AD is complex, driven by both environmental and genetic factors. Presently, aging and the gene encoding apolipoprotein allele E4² are the two largest known risk factors for sporadic AD. In contrast to sporadic AD, FAD is mostly driven by specific genetic mutations localized in at least 3 distinct genes, including those encoding the amyloid precursor protein (APP), Presenilin 1 and Presenilin 2. APP is important to all forms of AD because in addition to its specific involvement in the development of FAD, APP is the precursor of the A β peptides that aggregate to form the deposits of amyloid fibrils used to define this disorder. APP is also important to the neuropathology of Down syndrome because patients over the age of 40 years develop amyloid deposits identical to those found in patients with AD. Localization of the APP gene on chromosome 21 revealed a direct genetic linkage between these two disorders.³ A common theory posits that amyloid deposits of A β fibrils or soluble oligomeric forms of A β peptides are the main causes of the neurodegeneration of AD.⁴ There are several weaknesses to this theory however, including studies that show no significant correlation between brain amyloid loads and degree of dementia and data indicating that soluble A β species become toxic only at concentrations ten of thousand times higher than their *in vivo* concentrations (for recent review of involvement of A β and derivatives in AD see ref. 5). There are several weaknesses to this theory, however, including studies that show no significant correlation between the brain amyloid loads and the degree of dementia. Furthermore, soluble A β peptides are normal components of human serum and cerebrospinal fluid, and presently there is little evidence of disease-associated changes in soluble A β or its oligomeric forms. In this volume, Gandy and Lublin give a critical review of the involvement of soluble Oligomers in the development of AD.

Recent findings indicate that dysfunctions of the cerebrovascular system caused by cerebrovascular amyloidosis, oxidative stress, and genetics may play important roles in the pathogenesis of AD. Dickstein and colleagues offer an extensive analysis of factors that may promote cerebrovascular abnormalities and their potential involvement in AD. A recent theory suggests that the cellular process of autophagy, which functions to eliminate cellular waste, may also be involved in AD. In this volume, Funderburk *et al.* explore this topic and

offer an insightful description of the relationship between autophagy and neurodegeneration. Neuroinflammation and neurotoxicity have also been associated with AD, and many groups are actively examining the potential contribution of these processes to neuronal cell death in AD. Metcalfe and Pereira review this important topic in this volume. Transgenic animal models greatly facilitate studies of human disorders, and this technology has been used extensively to probe factors involved in neuronal dysfunction and behavioral abnormalities. Elder and colleagues cover this topic here.

The most important issue for AD patients and their families is therapeutic intervention. There is a clear need for more efficient therapeutics as currently available treatments provide largely symptomatic relief with only minor effects on the course of the disease. To this end, modern science employs an array of approaches, including immunomodulators, inhibitors of A β peptides, vaccination, anti-tau aggregation agents, neuroprotective factors, and anti-cholinergic agents. Two groups, one headed by Tom Wisniewski and the other by Mary Sano, review current efforts for the development of new therapeutics for AD.

REFERENCES

1. Glenner, G. A retrospective and prospective overview of the investigations on amyloid and amyloidosis – the β fibrilloses. In: Gleener, GG.; Costa, PP.; Freitas, FD., editors. Amyloid and Amyloidosis. Excerpta Medica; Amsterdam, the Netherlands: 1980. p. 3-13.
2. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993; 261:921–923. [PubMed: 8346443]
3. Robakis NK, Wisniewski HM, Jenkins EC, et al. Chromosome 21q21 sublocalization of the gene encoding the β -amyloid peptide present in cerebral vessels and neuritic (senile) plaques of people with Alzheimer disease and Down syndrome. Lancet. 1987;384–385. Lancet i. [PubMed: 2880184]
4. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002; 297:353–356. [PubMed: 12130773]
5. Robakis NK. Are A β and its Derivatives Causative Agents or Innocent Bystanders in AD? Neurodegenerative Dis. 2009 [Epub ahead of print].