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Alzheimer's disease: challenges ahead

Einar M. Sigurdsson*

Departments of Physiology and Neuroscience, and Psychiatry, New York University School of Medicine, New York, NY USA
**Correspondence: sigure01@nyumc.org*

Research on Alzheimer's disease (AD) has gone through periods of great enthusiasm with the view that its etiology and pathogenesis would be clarified in the near future. In recent years, a turning point was the discoveries in the nineties of mutations in the familial forms of the disease. A key development as well was the observation that the ε4 apolipoprotein E variant is a strong genetic risk factor for the late onset form of AD. Although these major findings have certainly shed some light on its causes and progression, it is disappointing that we do not fully understand their involvement in the disease, and the majority of AD cases have no clearly identified risk factors. Furthermore, these targets have yet to lead to the development of effective drugs, although it should be acknowledged that several clinical trials are underway. Based on available data from these studies, it appears that these experimental therapies are not likely to reverse the course of the disease but may perhaps stabilize it and/or delay its progression. To prevent it or postpone its onset, better diagnostic methods must be developed that are sufficiently sensitive and specific to detect the disease in its earliest stages prior to measurable cognitive deficits. A part of the problem is that AD may well be several different disorders with only a final common endpoint, namely loss of synapses, neurons and aggregation of amyloid-β and tau, with associated pathologies and cognitive impairments. Once these endpoint features have been established, it may be too late to figure out the originating defects and to do much about it. The presumably slow progression of AD, starting several years and even decades before clinical symptoms, make it particularly challenging to understand, diagnose early, and treat. Although several excellent animal models have been developed for this purpose, none recapitulate all the aspects of AD. It is therefore not surprising that several potential therapies that worked in animals have been ineffective in clinical trials.

In summary, the major challenges in the field are to: (1) Identify risk factors for the majority of the sporadic cases that are unrelated to apoE genotype; (2) Generate animal models with all the features of AD; (3) Detect individuals at risk prior to cognitive impairment, and; (4) Develop effective disease-modifying therapies. Even though numerous outstanding scientists and clinicians are working on solving these obvious problems with some promising recent findings, it is important to foster involvement of established investigators from other fields with unconventional ideas.

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