

## Alzheimer's Disease: Race against the Clock

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Alzheimer's disease (AD) is the most common cause of dementia. It is estimated that about 46.8 million persons are living with dementia and that this number is destined to double every 20 years, with a total worldwide cost of 818 billion dollars in 2015. Primary and secondary prevention, as well as innovative therapeutic intervention, reduce mortality from diseases such as cancer and circulatory accidents, but not from AD [1,2]. Studies on subjects from families affected by autosomal dominant AD (ADAD) allowed scientists to detect pathological hallmarks several years before the clinical onset of the disease. For this purpose, specific biomarkers were used [3]. Biomarkers detecting amyloid pathology (amyloid measurement in cerebrospinal fluid (CSF) and PET with tracers for beta-amyloid) are considered to be specific for AD. Less specific are tau concentration in CSF, <sup>18</sup>F-DG-PET and structural MRI [4]. Recent evidences led researchers to develop a hypothetical model of Alzheimer's disease, where dementia is the final stage of a process started many years earlier, with extracellular amyloid deposition followed by neuronal injury and death [5]. This is one possible explanation for the lack of efficacy of clinical trials involving mild to moderate dementia patients [6].

Recently, researchers are focusing their interests on preclinical stages of the disease. The idea is that we should deeply change our approach with AD, considering AD pathology detection sufficient to diagnose the disease [7]. Some important human disorders (i.e. diabetes mellitus, cancer, hypertension) could be diagnosed and treated in absence of clinical manifestation reducing significantly mortality and disability. Unfortunately, we are not able to predict the evolution of amyloid pathology to dementia yet. Longitudinal studies showed that ADAD mutations carriers failed on specific memory tasks many years before the clinical diagnosis of cognitive decline [7] and that neuropsychological measurement are as sensitive as biomarkers in detecting the disease [8]. Furthermore, subjective cognitive decline (SCD) has been recently defined as a condition characterized by individuals perceived changes in cognitive performances, in absence of objectively evidence [6]. Interestingly one study demonstrated that SCD correlates with amyloid burden [7]. This condition is now considered at risk of development of AD [6]. Some secondary prevention trials on preclinical ADAD or normal cognitive subjects with evidence of brain amyloid pathology are ongoing [9,10].

The hope is that in the future (how near?) AD will be diagnosed at first pathological stages and treated as well as we do now for other common human diseases.

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