ARE WE READY FOR PREVENTION TRIALS IN NON-SYMPTOMATIC INDIVIDUALS? THE TIME IS RIPE

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Alzheimer's disease (AD) was described by Alois Alzheimer in 1906 as a disease, associated with two neuropathological hallmarks. As much as the underlying pathology was clearly defined the diagnosis was purely based on the clinical syndrome for the next century. Resulting in a diagnosis of probable disease at a time when wide spread neurodegeneration has already occurred and neuronal loss results in measurable volume loss of the brain

Cognitive change is the most sensitive change early in the disease course; specifically amnestic memory deficit has been identified as an early indicator. Longitudinal studies have as well demonstrated that the process of cognitive decline accelerates towards the onset of the clinical syndrome.

Similarly biomarker studies like ADNI, AddNeuroMed and AIBL are underlying the development of disease models that integrate biological and clinical to hypothesize a 10-20 years period of disease development in the advent of dementia. Development of sensitive biomarkers for amyloid pathology (Amyloid-PET and CSF $A\beta_{1-42}$) have identified biomarker patterns specific for patients with AD and these biomarkers have been demonstrated to be predictive for the development of the disease. Resulting new diagnostic criteria have been developed for different stages of the disease by international expert groups, led by the US National Institute for Aging and the International Working Group. Specifically focusing on these earliest subjects in the continuum of the AD disease process three stages can be identified in asymptomatic subjects: (1) Pathologic Amyloid biomarker, (2) pathologic Amyloid biomarker and positive marker of neurodegeneration and (3) pathologic Amyloid biomarker, positive marker of neurodegeneration and evidence of subtle cognitive change.

Implementing these new criteria in data e.g. from the Mayo Clinic and Washington University, has demonstrated the validity of the concept and revealed surprisingly similar results on progression patterns and clinical characteristics of these subjects.

So understanding how to define the population, the resulting question is do we have measures and trial designs available to test a treatment hypothesis. Sensitive cognitive tools have been proposed and shown concept validity in observational trials. The proof of sensitivity for treatment effect will only be possible in the coming clinical trials. The first trial in this respect is the Anti-Amyloid Treatment in Asymptomatic Alzheimer's study (A4 study).

In conclusion, understanding of the disease continuum and the use of biomarkers to identify subjects early has fostered the concepts of early pre-dementia Alzheimer's disease. These patient groups are ideal to target secondary prevention in Alzheimer's disease today.