Is it Possible to Prevent Progression from MCI to Alzheimer Disease?

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Abstract
The recent emphasis in Alzheimer’s Disease (AD) clinical research is on early disease detection, with the hope of early treatment to slow progression of AD could prevent many individuals from developing symptoms and save billions of dollars in health care costs.

Introduction
The concept of mild cognitive impairment (MCI) as a phase between normal aging, early dementia, and AD has served as an added stimulus for early detection. The term MCI was initially used by Flicker et al. [1] who showed progression to a dementia in a group of elderly subjects who were longitudinally followed and initially had mild impairment on psychometric tests when compared with controls. Subsequently, Petersen RC and Petersen RC et al. [2,3] refined the concept in more detail. Amnestic MCI is characterized by memory impairment, objective evidence of memory impairment for age and education, intact general cognitive function, minimal changes in activities of daily living, and lack of dementia. Other forms of MCI exist, including multiple-domain and single non memory-domain types, but amnestic MCI appears to be the most common form [4].

Descriptions of the rate of the progression of MCI and the stability of MCI as a syndrome vary considerably across different studies, in part because of differing subject populations [5-10]. Recent reports from autosomal dominant forms of Alzheimer’s Disease (AD) suggest that amyloid-β (Aβ) accumulation may be evident 20 years before the stage of dementia and that there is already substantial neuronal loss by the stage of Mild Cognitive Impairment (MCI). Indeed, this long, inexorable progression of neurodegeneration, that is well entrenched by the stage of symptomatic disease, may account, at least partially, for our failure to develop successful disease-modifying therapies [11].

Discussion
A widely accepted assumption is that AD begins with abnormal processing of amyloid precursor protein (APP), which then leads to excess production or reduced clearance of β-Amyloid (Aβ) cortex. All known forms of autosomal-dominant AD involve genes that either encode APP itself, or encode protease subunit (PS1 and PS2) that are involved in the cleavage of Aβ from APP to generate amyloidogenic Aβ peptides. By unknown mechanisms, but possibly as a result of the toxic effects of Aβ oligomers, one or more forms of Aβ leads to a cascade characterized by abnormal tau aggregation, synaptic dysfunction, cell death, and brain shrinkage. The abnormal protein deposits that characterize AD pathologically are well known: Aβ plaques and Neurofibrillary Tangles (NFTs) formed by hyperphosphorylated tau.

Neurodegeneration is as important as these hallmark pathological lesions of AD, and manifests as atrophy, neuron loss, and gliosis, which are routinely noted in research post-mortem examinations.

There is strong evidence that MRI, FDG-PET, and CSF tau biomarkers are already abnormal in patients who are in the MCI phase of AD. Abnormalities in neurodegenerative AD biomarkers also precede the appearance of the first cognitive symptoms. Of the three Neurodegenerative biomarkers, evidence that FDG-PET abnormalities precede any cognitive symptoms in individuals who later progress to AD is probably the strongest. However, rates of atrophy on MRI do become abnormal in cognitively normal individuals who later progress to AD. Thus, the available data strongly support the conclusion that abnormalities in both Aβ and neurodegenerative biomarkers precede clinical symptoms. On the basis of the evidence presented above, we propose the use of specific AD biomarkers for disease staging in vivo [12]. The disease model and biomarker staging are shown in Figure 1, which embodies the following set of principles.

First, the biomarkers become abnormal in a temporally ordered manner as the disease progresses. Second, Aβ-plaque biomarkers are dynamic early in the disease, before the appearance of clinical symptoms, and largely reached a plateau by the time clinical function, and symptoms later. Third, biomarkers of neural injury, dysfunction is dynamic later in the disease and correlate with clinical symptom severity [13].

The Entorhinal Cortex (EC) plays a crucial role as a gateway connecting the neocortex and the hippocampal formation. Layer II of the EC gives rise to the perforant pathway, the major source of the excitatory input to the hippocampus, and layer IV receives a major hippocampal afferent projection. The EC is affected severely in AD,
likely contributing to memory impairment. We applied stereological principles of neuron counting to determine whether neuronal loss occurs in the EC in the very early stage of AD, had 32% fewer EC neurons than controls. Decreases in individual lamina were even more dramatic, with the number of neurons in layer II decreasing by 60% and in layer IV by 40% compared with controls [14].

In a study of patients who were followed longitudinally and had CDR scores 0.5, Price and Morris [15] found that all of patients had the neuropathologic changes of AD. They also found neocortical and limbic DP diffuse plaques, NP (neuritic plaques), and NFTs (neurofibrillary tangles) in non-demented cases and suggested that the patients had preclinical AD. Morris et al. [16] found that a series of subjects with CDR scores of 0.5 with uncertain dementia at entry into their study and another group with CDR scores of 0.5 with incipient AD at entry almost always had neuropathologic features of AD at autopsy. In another brief description of 11 subjects with the clinical diagnosis of MCI, 5 had AD-like pathology with NFTs in medial temporal lobe and a moderate number of DPs and sparse NPs in the neocortex. Petersen et al. and Markesbery et al. [17,18] indicated that in patients with amnestic MCI who were followed longitudinally, the early changes of AD were present. From a neuropathologic perspective, they were in agree ment with Morris and Price [6], who suggested that amnestic MCI, is in reality, early AD.

Conclusion
AP accumulates for well over a decade and the neurodegeneration that occurs downstream of AP accumulation is well entrenched even prior to MCI. Therefore, it is possible that treatments that remove all toxic AP species from the brain still will not alter the clinical course of the disease after significant neuronal injury [19].

We would like to move our diagnostic criteria into the asymptomatic range to capture people who are clinically normal but at risk for developing AD in the future. As such the proposed outline for enhancing the specificity of MCI could be applied to the asymptomatic stage of the aging continuum and enhance ability to develop compounds to prevent the disorder before the destruction of neuronal tissue has occurred [20].

References