Secondary prevention of Alzheimer's dementia: neuroimaging contributions

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Abstract:

Background: In Alzheimer's disease (AD), pathological changes may arise up to 20 years before the onset of dementia. This pre-dementia window provides a unique opportunity for secondary prevention. However, exposing non-demented subjects to putative therapies requires reliable biomarkers for subject selection, stratification, and monitoring of treatment. Neuroimaging allows the detection of early pathological changes, and longitudinal imaging can assess the effect of interventions on markers of molecular pathology and rates of neurodegeneration. This is of particular importance in pre-dementia AD trials, where clinical outcomes have a limited ability to detect treatment effects within the typical time frame of a clinical trial. We review available evidence for the use of neuroimaging in clinical trials in pre-dementia AD. We appraise currently available imaging markers for subject selection, stratification, outcome measures, and safety in the context of such populations.

Main body: Amyloid positron emission tomography (PET) is a validated in-vivo marker of fibrillar amyloid plaques. It is appropriate for inclusion in trials targeting the amyloid pathway, as well as to monitor treatment target engagement. Amyloid PET, however, has limited ability to stage the disease and does not perform well as a prognostic marker within the time frame of a pre-dementia AD trial. Structural magnetic resonance imaging (MRI), providing markers of neurodegeneration, can improve the identification of subjects at risk of imminent decline and hence play a role in subject inclusion. Atrophy rates (either hippocampal or whole brain), which can be reliably derived from structural MRI, are useful in tracking disease progression and have the potential to serve as outcome measures. MRI can also be used to assess comorbid vascular pathology and define homogeneous groups for inclusion or for subject stratification. Finally, MRI also plays an important role in trial safety monitoring, particularly the identification of amyloid-related imaging abnormalities (ARIA). Tau PET to measure neurofibrillary tangle burden is currently under development. Evidence to support the use of advanced MRI markers such as resting-state functional MRI, arterial spin labelling, and diffusion tensor imaging in pre-dementia AD is preliminary and requires further validation.

Conclusion: We propose a strategy for longitudinal imaging to track early signs of AD including quantitative amyloid PET and yearly multiparametric MRI.

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