ELSEVIER

Alzheimer's & Dementia 10 (2014) 666-674

Alzheimer's & Dementia

An empirically derived composite cognitive test score with improved power to track and evaluate treatments for preclinical Alzheimer's disease

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Abstract

Background: There is growing interest in the evaluation of preclinical Alzheimer's disease (AD) treatments. As a result, there is a need to identify a cognitive composite that is sensitive to track preclinical AD decline to be used as a primary endpoint in treatment trials.

Methods: Longitudinal data from initially cognitively normal, 70- to 85-year-old participants in three cohort studies of aging and dementia from the Rush Alzheimer's Disease Center were examined to empirically define a composite cognitive endpoint that is sensitive to detect and track cognitive decline before the onset of cognitive impairment. The mean-to-standard deviation ratios (MSDRs) of change over time were calculated in a search for the optimal combination of cognitive tests/subtests drawn from the neuropsychological battery in cognitively normal participants who subsequently progressed to clinical stages of AD during 2- and 5-year periods, using data from those who remained unimpaired during the same period to correct for aging and practice effects. Combinations that performed well were then evaluated for representation of relevant cognitive domains, robustness across individual years before diagnosis, and occurrence of selected items within top performing combinations.

Results: The optimal composite cognitive test score comprised seven cognitive tests/subtests with an MSDR = 0.964. By comparison, the most sensitive individual test score was Logical Memory Delayed Recall with an MSDR = 0.64.

Conclusions: We have identified a composite cognitive test score representing multiple cognitive domains that has improved power compared with the most sensitive single test item to track preclinical AD decline and evaluate preclinical AD treatments. We are confirming the power of the composite in independent cohorts and with other analytical approaches, which may result in refinements, have designated it as the primary endpoint in the Alzheimer's Prevention Initiative's preclinical treatment trials for individuals at high imminent risk for developing symptoms due to late-onset AD.

Keywords: Preclinical Alzheimer's disease; Cognition; Prevention; Clinical trials; Composite endpoints; Power; Sample size

Portions of this study were presented at the 2011 Alzheimer's Association International Conference, Paris, France, and the 2011 Clinical Trials on Alzheimer's Disease, San Diego, CA.

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http://dx.doi.org/10.1016/j.jalz.2014.02.002

1. Introduction

Without an effective treatment that postpones the onset or completely prevents the clinical consequences of Alzheimer's disease (AD), the number of individuals afflicted by the disease will continue to rapidly increase [1,2]. There is growing interest in the hypothesis that interventions may have their most profound effect if initiated in the preclinical AD phase [3], that is, in the absence of mild cognitive impairment (MCI) or AD dementia [4]. Several such trials are underway or are in various planning stages, including those with the strategy of testing therapies in people who are at highest imminent risk of developing MCI or AD dementia because of factors such as age and genetic disposition or presence of biomarker evidence of AD [4–8]. Traditional clinical outcomes such as progression to clinical diagnosis or cognitive outcomes developed for studies in MCI or AD dementia may not be well suited for some preclinical treatment trials because of large sample size and long trial duration requirements or the psychometric properties of the tests themselves [9–12]. Moreover, individually examining each cognitive assessment and treating as individual outcomes inflate type I error if appropriate corrections are not made to guard against multiple comparisons. Use of an appropriate composite reduces the number of variables used and thus the risk of type I error; it can be empirically derived; and its sensitivity to detect and track preclinical AD can be validated in multiple data sets. As a result, it affords a measure of multiple domains that can serve as a primary endpoint in preclinical treatment trials [13].

Small, but measurable, cognitive decline occurs during preclinical AD. For instance, retrospective and prospective studies of cognitively healthy individuals who eventually progressed to AD dementia have shown episodic memory decline to be a defining feature of preclinical AD [14–18]. In addition, decline in other cognitive domains such as executive [19], visual spatial [16], and global cognitive functioning [16,20] occurs during the transition from normal aging to preclinical AD and into the clinical stages of AD. Studies of cognitively healthy individuals with significant fibrillar amyloid burden report decline primarily in episodic memory, executive function, and language [21–25]. Long-term recall memory performance has been found to begin to decline in relationship to apolipoprotein E (*APOE*) ε4 gene dose, reflecting three levels of genetic risk for late-onset AD, despite maintenance of normal clinical status [26].

There are multiple approaches for selecting an appropriate cognitive endpoint for use in preclinical AD studies and therapeutic trials. For instance, a theoretically driven approach reasons that a composite should be constructed a priori from cognitive assessments known to decline during preclinical AD. A related approach is to construct composites specific to individual cognitive domains such as memory [27] or executive functioning [28]. Yet another is an empirically driven approach, in which the endpoint or composite is selected based on analyses demonstrating sensitivity (e.g., has the greatest power) to detect and track the outcome of interest such as preclinical AD decline. These approaches are not necessarily mutually exclusive; for instance, theoretical knowledge of preclinical AD can be taken into account when empirically deriving a composite cognitive test score. Several different analysis methods are available to develop composites, including but not limited to latent variable analyses or partial least squares regression [29–31], principal components [32], item response theory [33], Rasch measurement theory [34], or item-level analysis [35]. Although there have been some efforts focused on refining existing cognitive assessments, this may be best suited for MCI and early AD trials [36].

Here, we propose a strategy to empirically determine the combination of cognitive assessments most sensitive to track preclinical AD in individuals who subsequently progress to MCI or probable AD dementia, while controlling for practice and normal aging effects using data from individuals who did not progress to the clinical stages of AD over the same duration. The goal of the present study was to develop a composite with optimal sensitivity to decline, not limited to a single cognitive domain, corresponding to a change from baseline analysis. This approach differs from optimizing an endpoint for discriminating those who progress from those who remain stable, which would result in a composite that could be used as a progression endpoint in preclinical treatment trials. We hypothesize that the composite will be more sensitive (i.e., have greater power) to detect and track preclinical AD decline compared with the most sensitive individual cognitive test/subtest score given that the approach allows for the addition of assessments that improve sensitivity overall, despite perhaps being less sensitive individually to preclinical AD decline. Longitudinal data from three cohort studies of aging and dementia at the Rush Alzheimer's Disease Center in those who did and did not clinically progress over 2- and 5-year periods were used to develop a composite cognitive test score, using the mean-to-standard deviation ratio (MSDR) of the change score as the measure of sensitivity to preclinical AD decline over time [31]. The results from the present study are informing the design of trials for the Alzheimer's Prevention Initiative (API) focused on individuals at high imminent risk for symptoms of late-onset AD based on their age and genetics.

2. Materials and methods

2.1. Participants

Data from participants enrolled in the Rush Alzheimer's Disease Center's Religious Orders Study (ROS), Memory and Aging Project (MAP), or the Minority Aging Research Study (MARS) were downloaded on June 7, 2010. Enrollment criteria for the three studies are quite similar and