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Five-year biomarker progression variability for Alzheimer's disease dementia prediction: Can a complex instrumental activities of daily living marker fill in the gaps?

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Abstract

Introduction: Biomarker progressions explain higher variability in cognitive decline than baseline values alone. This study examines progressions of established biomarkers along with a novel marker in a longitudinal cognitive decline.

Methods: A total of 215 subjects were used with a diagnosis of normal, mild cognitive impairment (MCI) or Alzheimer's disease (AD) at baseline. We calculated standardized biomarker progression rates and used them as predictors of outcome within 5 years.

Results: Early cognitive declines were more strongly explained by fluorodeoxyglucose-positron emission tomography, precuneus and medial temporal cortical thickness, and the complex instrumental activities of daily living (iADL) marker progressions. Using Cox proportional hazards model, we found that these progressions were a significant risk factor for conversion from both MCI to AD (adjusted hazard ratio 1.45; 95% confidence interval 1.20–1.93; $P = 1.23 \times 10^{-5}$) and cognitively normal to MCI (adjusted hazard ratio 1.76; 95% confidence interval 1.32–2.34; $P = 1.55 \times 10^{-5}$).

Discussion: Compared with standard biological biomarkers, complex functional iADL markers could also provide predictive information for cognitive decline during the presymptomatic stage. This has important implications for clinical trials focusing on prevention in asymptomatic individuals.

Keywords: Computerized cognitive assessment; Rate of progression; Diagnostics; Early detection; Biomarker; Biomarker progressions; Cognitive declines; MCI; MRI; PET; Alzheimer's disease

1. Introduction

Accurate and early Alzheimer's disease (AD) staging and differential diagnosis possess a pressing modern challenge, partly fueled by recent AD disease-modifying treatment paradigms that only work if applied during the presymptomatic phase [1]. Accurate and earlier diagnosis of patient states is difficult, partly because, despite the popularity of the AD cascade model [2], amyloid and tau-based, pathologic progressions, such as neuritic plaques and neurofibrillary pathology, are interacting in a much more complex way than previously thought [3]. The complexity of the AD pathologic events is now accepted to occur years before symptomatic onset and it challenges current knowledge of the underlying

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pathologic pathways [4]. Determining new diagnostic criteria that incorporate biomarkers to construct models of disease progression enabled the mechanism to stage and stratify patients during the presymptomatic phase [5]. For example, the revised National Institute on Aging -Alzheimer's Association (NIA-AA) criteria [6] helped reduce heterogeneity in trial groups, monitor treatment outcomes, and match persons to presumptive treatments. However, despite the deeper understanding and availability of AD in vivo biomarkers, the evidence base for this is relatively limited [7]. A major challenge is to construct models of disease progression that estimate biomarker ordering and dynamics directly from real-world data sets enabling quantitative evaluation of the disease since its earliest stages [8]. At the presymptomatic stage, this would mean to allow the capturing of healthy individuals at risk of developing AD.

Hypothetical models of AD progression have been proposed that describe presymptomatic sequences in which different biomarkers become abnormal [9]. The most well validated of these models generally propose that cerebrospinal fluid (CSF) amyloid pathology and amyloid positron emission tomography (PET) abnormalities precede CSF phosphorylated and total tau (t-tau), fluorodeoxyglucose-positron emission tomography (FDG-PET) hypometabolism, and measures of brain metabolism precede regional neurodegeneration, e.g., volume and atrophy rate markers derived from structural magnetic resonance (MRI), which all occur before a significant clinical change in cognitive performance test scores [10]. When attempting to validate the ordering of these biomarkers, e.g., Brickman et al. [11], CSF brain amyloidosis, neuronal degeneration, namely elevated CSF tau protein, decreased cortical FDG-PET, and medial temporal atrophy on MRI, the results are always dependent on defining abnormal biomarker levels and choosing cut points, which are not easy to establish. Others are also attempting to determine biomarker ordering using a priori staging based on clinical diagnosis and not informed directly by measured data sets [12]. Such attempts can only provide ordering of a small number of biomarkers and limit the temporal resolution of such models to crude stages (e.g., normal, early mild cognitive impairment [MCI], late MCI, or AD). For instance, empirically derived MCI stages or subtypes demonstrate heterogeneity that is not captured by conventional criteria in MCI cognitive profiles. Conventional profiles are susceptible to false-positive errors, which implicates the result of prior MCI studies and may be diluting important biomarker relationships [13]. Moreover, because the way a biomarker is measured can make a difference in diagnostic accuracy, harmonized protocols are still needed [14–16].

In the context mentioned previously, a recently introduced, probabilistic, event-based model (EBM) provided a generative model of AD progression, as a sequence of events, at which individual biomarkers become abnormal. Recent work [17] demonstrated the EBM's consistent ability to learn normal and abnormal distributions of presymptomatic AD biomarker values from data, without requiring any a priori staging or cut points. Researchers might be using such an approach to stage subjects retrospectively and follow a large elderly cohort over a long period of time. For example, Rembach et al. [18] showed such an analysis in plasma amyloid beta and Lim et al. [19] estimated the rate of change of prodromal AD biomarkers and obtained an average cognitive trajectory over time. Similarly, Tarnanas et al. [20] showed a 2-year rate of change but with the introduction of a novel computer-based marker along with MRI and event-related potential biomarkers in subjects with MCI. However, although a promising approach, one issue not systematically examined previously is whether biomarker changes from baseline value to end point or biomarker changes over all the intermediate time points (referred in this study as biomarker progressions) were more strongly associated with cognitive declines. A recent study [21] examined the relative ability of baseline values versus biomarker progressions at each stage of AD in predicting cognitive declines and proved that progressions explained higher variability in cognitive declines than values at the baseline. This finding provides an improved model of the longitudinal, nonlinear association between biomarker and regional atrophy progressions and shows that future clinical trials would benefit by identifying such biomarker progressions most strongly associated with cognitive and functional declines at later stages [22].

Given the amount of recent accumulated knowledge on normal and abnormal function of biomarker progressions, it is not surprising that computer-processable disease models are taking the lead in drug and biomarker discovery efforts [23]. As an illustration [24], proposed two computer-processable cause-and-effect models are based on the Biological Expression Language (http://www.openbel.org/), which support the automatic reasoning of interlinked molecules, and normal and abnormal biological processes. They argued that computer-processable disease models should be based on cause-and-effect regulatory effects that link upstream causal entities to downstream bioclinical effects. In agreement with that group, we believe that computer-processable disease model approaches would be enhanced with the addition of quantitative, real-life, complex activities of daily living, a computerized cognitive performance data set, such as our complex instrumental activities of daily living (iADL) marker with day-out task (DOT) and dual-task walk (NAV) profiles.

The aim of this study was to examine the relative ability of individual biomarker progressions in relation to our complex iADL marker of longitudinal cognitive and functional declines. We used 5-year longitudinal data at each stage of AD to assess which progressions are associated with such declines. To conduct a fair comparison, analogous to a recent study [21], we standardized all biomarkers and presented