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The Alzheimer's Disease Neuroimaging Initiative 2 Biomarker Core: A review of progress and plans

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Abstract

Introduction: We describe Alzheimer's Disease Neuroimaging Initiative (ADNI) Biomarker Core progress including: the Biobank; cerebrospinal fluid (CSF) amyloid beta ($A\beta_{1-42}$), t-tau, and p-tau_{181} analytical performance, definition of Alzheimer's disease (AD) profile for plaque, and tangle burden detection and increased risk for progression to AD; AD disease heterogeneity; progress in standardization; and new studies using ADNI biofluids.

Methods: Review publications authored or coauthored by ADNI Biomarker core faculty and selected non-ADNI studies to deepen the understanding and interpretation of CSF $A\beta_{1-42}$, t-tau, and p-tau_{181} data.

Results: CSF AD biomarker measurements with the qualified AlzBio3 immunoassay detects neuropathologic AD hallmarks in preclinical and prodromal disease stages, based on CSF studies in non-ADNI living subjects followed by the autopsy confirmation of AD. Collaboration across ADNI cores generated the temporal ordering model of AD biomarkers varying across individuals because of genetic/environmental factors that increase/decrease resilience to AD pathologies.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Discussion: Further studies will refine this model and enable the use of biomarkers studied in ADNI clinically and in disease-modifying therapeutic trials.

Keywords: Alzheimer's disease; Mild cognitive impairment; Cerebrospinal fluid; Plasma; Biomarkers; Immunoassay; ADNI; Disease-modifying therapy; $A\beta_{1-42}$; Tau

1. Introduction

Alzheimer's disease (AD), the most common form of dementia [1,2]. It is a complex progressive neurodegenerative disease that leads to the loss of memory and cognitive function. The disease is pathologically characterized by amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) that are composed largely of fibrillar forms of Aβ and hyperphosphorylated tau (p-tau), respectively. During the past two decades cumulative molecular and clinical studies have provided evidence for our understanding of the molecular characteristics and progressive pathologic features of AD. These pathologic changes are reflected in cerebrospinal fluid (CSF), respectively, by lowered levels of $A\beta_{1-42}$ followed by increased total tau (t-tau) or p-tau_{181}. In the Biomarker Core of the Alzheimer's Disease Neuroimaging Initiative (ADNI-1) located at the Perelman School of Medicine of the University of Pennsylvania (Penn), we defined cut points for the use of these biomarkers and their ratios using an ADNI-independent autopsy-based Penn AD cohort and age-matched living normal control (NC) subjects. Cognitive decline in AD patients closely correlates to neurofibrillary tangles (NFTs), synapse loss, and neurodegeneration [3–5]. However, there is a growing awareness for the occurrence of one or more copathologies in sporadic AD including Lewy bodies (LBs), vascular disease, transactive response DNA binding protein 43 kDa (TDP-43) inclusions, and hippocampal sclerosis which most likely contributes to the variable timeline for the progression of AD [6] as reflected in the imaging, CSF biomarkers, and clinical features of patients with dementia of the AD type (DAT) (Fig. 1).

AD can be divided into different phases: (1) a preclinical phase in which subjects are cognitively normal but have mild AD pathology, (2) a prodromal phase known as mild cognitive impairment (MCI), and (3) a phase when patients show dementia with impairments in multiple domains and loss of function in activities of daily living [4,7–9]. On the basis of the prevailing scientific evidence, CSF $A\beta_{1-42}$ and the tau proteins have been incorporated into the revised research diagnostic criteria for AD together with β-amyloid positron emission tomography (PET) imaging [10–13], and tau amyloid PET imaging is now also available [14,15]. It is being added to the ADNI portfolio of imaging technologies. ADNI-1 studies reported evidence of AD pathology in one-third of the cognitively intact elderly NC subjects solely based on CSF $A\beta_{1-42}$ [16,17]. It is time to consider developing strategies to identify AD at the presymptomatic and prodromal phases to optimize the potential efficacy of disease-modifying therapies, and to enable drug development aimed at AD prevention. A key goal of ADNI continues to be the improvement of the standardization of biomarker measurements to enable their use in clinical AD trials, across multiple testing laboratories, and in routine clinical practice. Thus, the standardization of both preanalytical (at the level of biofluid sample collection, handling, aliquot preparation, and storage) and analytical sources of variability continues to be a priority of the Penn Biomarker Core and we continue to collaborate with biomarker scientists on these issues. We participated in recent consensus group and we are part of the Alzheimer's Biomarker Standardization Initiative, providing a set of recommendations for 10 preanalytical factors [18]. We have continued the work of analytical method standardization in the Penn Biomarker Core of ADNI and also have collaborated with colleagues in the Global Biomarker Standardization Consortium (GBSC) in support of $A\beta_{1-42}$ calibrator standardization, based on mass spectrometry, across various immunoassay platforms [19]. We expect that an outcome of all these efforts will be the availability of the most highly standardized methods for CSF $A\beta_{1-42}$ and tau proteins. In this review, we summarize progress by the Penn Biomarker Core of ADNI using the developed pathological CSF biomarker profile that sensitively detects Aβ amyloid plaque burden (below the threshold for the CSF $A\beta_{1-42}$ concentration) and NFTs, synapse loss, and neurodegeneration (above-threshold for CSF tau protein concentrations) [16]. We continue the collaborative work to develop biomarker tests for α-synuclein (α-syn) to indicate the presence of concomitant LBs and for TDP-43 as an indicator of inclusions of this biomarker in early AD, early and late MCI, and NC subjects. The Penn Biomarker Core has collaborated with other ADNI Cores in multimodal data analyses across ADNI to temporally order changes in clinical measures, imaging data, and chemical biomarkers that refine and expand our understanding and interpretation of the pathophysiology involved in the disease progression from NC to MCI and from MCI to AD. The hypothetical model of the temporal evolution of changes in the AD biomarkers will be further developed within the Biomarker Core studies in the ADNI-2 grant (Fig. 1) and informs our plans for the ADNI-3 competing renewal application.

2. Biofluid repository update

2.1. Overview

From 2010 through 2015, the ADNI-1 and II biofluid repository at Penn continuously receives biofluids (CSF,