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CSF Biomarkers

Cerebrospinal fluid ratios with $A\beta_{42}$ predict preclinical brain β-amyloid accumulation

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Abstract

Introduction: Biomarkers are urgently needed for the critical yet understudied preclinical stage of Alzheimer's disease (AD).

Methods: Cerebrospinal fluid (CSF) collection, [C-11]Pittsburgh compound B (PiB) amyloid imaging, and magnetic resonance imaging were acquired in 104 cognitively healthy adults enriched with risk for sporadic AD. Image-derived cerebral β-amyloid (Aβ) burden, measured concurrently and longitudinally, was regressed on CSF measures of Aβ, neural injury, and inflammation, as well as ratios with $A\beta_{42}$. Linear mixed-effects regression was used to model the effect of the CSF measures that predicted longitudinal brain amyloid accumulation on longitudinal cognitive decline, measured by memory test scores.

Results: At baseline, $A\beta_{42}/A\beta_{40}$ and all CSF ratios to $A\beta_{42}$ were associated with PiB binding in AD-vulnerable regions. Longitudinally, $A\beta_{42}/A\beta_{40}$ and ratios of total tau (t-tau), phosphorylated-tau (p-tau), neurofilament light protein, and monocyte chemoattractant protein-1 to $A\beta_{42}$ were associated with increased Aβ deposition over 2 years, predominantly in lateral parietal and temporal cortex. However, these CSF ratios were not significantly associated with cognitive decline, and the effect seems to be largely driven by $A\beta_{42}$ in the denominator.

Discussion: These results corroborate previous findings that t-tau/$A\beta_{42}$ and p-tau/$A\beta_{42}$ are the strongest candidate biomarkers during the preclinical time frame. They support a framework in which neural injury and amyloid deposition are likely occurring simultaneously. It may be that neurodegenerative processes influence progressive amyloid accumulation, even in the preclinical

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time frame. CSF biomarkers for nonspecific axonal injury and inflammation may provide more information at more advanced stages of the preclinical time course.

Keywords: Amyloid; PiB; PET; Cerebrospinal fluid; Biomarkers; Preclinical AD; Alzheimer's disease; Biological parametric mapping; Aβ42; Tau; NFL; MCP-1; YKL-40; Linear mixed-effects

1. Introduction

Although it is widely accepted that Alzheimer's disease (AD) pathology, including β-amyloid (Aβ) deposition in plaques and microvessels and tau pathology in the form of neurofibrillary tangle formation, begins decades before symptom onset [1–4], there is a paucity of longitudinal research in the late mid-life time frame [1] necessary to establish this effect empirically. Greater understanding of biomarkers associated with these hallmark features of AD, including tau and Aβ proteins in cerebrospinal fluid (CSF) and in-vivo neuroimaging measures of Aβ burden, during preclinical stages is important for early detection and future treatment and prevention efforts [1,2,5].

The most widely accepted model of AD etiology proposes that amyloid deposition in the brain is an early and critical step in driving the pathophysiological processes of AD that in turn initiate neurodegeneration, in the form of synaptic failure and neuronal death, and eventual symptom manifestation [1,6,7]. Increasing evidence suggests that amyloid may be necessary—although even this is contested by some [8]—but not sufficient for developing AD [6,8–11]. Aβ may be neither the primary nor the only neurotoxin that causes AD; but it is likely the key initiator of many complex, often tau-dependent, pathologic changes in the brain culminating in neurodegeneration years later [12]. In accordance with this theory, recent in vitro and in vivo work demonstrates a dynamic positive feed-forward mechanism whereby Aβ drives the disease pathway through tau, and tau further increases Aβ levels [13]. Aβ imaging by itself is not sufficient for a clinical prognosis in the preclinical time frame, and it may be that the most promising AD biomarkers will encompass multiple aspects of the disease, including amyloid and tau-mediated neural injury.

Because of the molecular exchange of metabolites between the brain and CSF, CSF analytes reflect biochemical and pathologic processes in the brain [5,14,15], thereby providing means for examining multiple indicators of disease processes occurring in the central nervous system. CSF Aβ and tau have high diagnostic accuracy for AD [16], but their reliability for the detection of possible preclinical AD is still unclear.

To examine features associated with spatial amyloid binding and longitudinal accumulation in the preclinical time frame, we conducted a multimodal study with Pittsburgh compound B (PiB) positron emission tomography (PET) imaging and CSF biomarkers in a late middle-aged, cognitively healthy sample enriched with the risk factors of apolipoprotein E ε4 (*APOE* ε4) genotype and parental history of sporadic AD from the Wisconsin Registry for Alzheimer's Prevention (WRAP; [17]). Our study had three aims as follows: (1) investigate relationships between amyloid pathology in the brain and concurrent CSF biomarkers associated with amyloid deposition, neuronal injury, and inflammation; (2) determine whether CSF biomarker levels at baseline lumbar puncture (LP) predict changes in PiB amyloid deposition over a subsequent 2-year period; and (3) investigate relationships between CSF predictors of brain Aβ and longitudinal cognitive decline.

We hypothesized that CSF biomarkers of AD pathology including amyloid burden (lower $A\beta_{42}$), tangle pathology (elevated phosphorylated-tau [p-tau]), axonal injury (elevated total-tau [t-tau] and neurofilament light protein [NFL]), and microglial activation/inflammation (elevated monocyte chemoattractant protein 1 [MCP-1] and chitinase-3–like protein [YKL-40]) would be associated with greater amyloid deposition at baseline and greater longitudinal amyloid accumulation over 2 years. We further hypothesized that $A\beta_{42}$ ratios (e.g., t-tau/$A\beta_{42}$) would most likely be associated with cognitive decline, as ratios reflect multiple AD-related pathologies simultaneously, suggesting greater risk for imminent disease.

2. Material and methods

Extended materials and methods are included as Supplementary Material.

2.1. Participants

Participants in this study were recruited from WRAP [17] if they had participated in biomarkers substudies. For this analysis, subjects were included if they had one or more amyloid and magnetic resonance imaging (MRI) scans, and CSF collected at the time of the first amyloid scan, resulting in a sample of 104. The University of Wisconsin Institutional Review Board approved all study procedures, and each subject provided signed informed consent before participation.

2.2. Biomarker collection

All participants underwent baseline MRI, [C-11]PiB PET, and LP as described previously [18,19]. A total of 78 additionally underwent a second PiB scan approximately 2 years later. The first visit at which amyloid scans, MRI