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Blood-Based Biomarkers

Plasma amyloid β 42/40 ratios as biomarkers for amyloid β cerebral deposition in cognitively normal individuals

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Abstract

Introduction: Plasma amyloid β (Aβ) peptides have been previously studied as candidate biomarkers to increase recruitment efficiency in secondary prevention clinical trials for Alzheimer's disease.

Methods: Free and total Aβ42/40 plasma ratios (FP42/40 and TP42/40, respectively) were determined using ABtest assays in cognitively normal subjects from the Australian Imaging, Biomarker and Lifestyle Flagship Study. This population was followed-up for 72 months and their cortical Aβ burden was assessed with positron emission tomography.

Results: Cross-sectional and longitudinal analyses showed an inverse association of Aβ42/40 plasma ratios and cortical Aβ burden. Optimized as a screening tool, TP42/40 reached 81% positive predictive value of high cortical Aβ burden, which represents 110% increase over the population prevalence of cortical Aβ positivity.

Discussion: These findings support the use of plasma Aβ42/40 ratios as surrogate biomarkers of cortical Aβ deposition and enrichment tools, reducing the number of subjects submitted to invasive tests and, consequently, recruitment costs in clinical trials targeting cognitively normal individuals.
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Keywords: Amyloid β; Plasma amyloid β ratio; Biomarker; Preclinical Alzheimer's disease; β-Amyloid imaging; Positron emission tomography; Clinical trials

1. Introduction

Dementia is a major public health problem worldwide, which currently affects 46 million people, a number estimated to increase up to 131.5 million by 2050, entailing an enormous social and financial burden [1]. Alzheimer's disease (AD) accounts for 60% to 70% of all cases of dementia; thus, the benefits of a successful therapeutic intervention that could stop or, ideally, prevent the development of AD are undeniable. However, therapeutic trials have had limited success so far, partly because of the advanced neurodegenerative stage of individuals typically targeted in clinical trials over the last two decades. Considering that the efficacy of potential AD treatments would likely depend on an early intervention, there is a growing need for accurate identification of asymptomatic (preclinical) individuals with underlying pathology for inclusion in the current and more favored secondary prevention trials [2–4].

Conflicts of interest: The authors have no conflicts of interest related to this work.

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Consequently, considerable investigational effort has been devoted in recent years to identify biological markers indicative of preclinical and/or prodromal AD before the onset of dementia [5,6]. This new concept of AD has also emphasized the importance of biomarkers as eligibility criteria to enrich clinical trial cohorts with subjects at increased risk of suffering more rapid cognitive decline. Amyloid β (Aβ) is the most likely cause of the pathophysiological process leading to AD dementia and, consequently, Aβ-related biomarkers should be ideal for the identification of the earliest stages of the disease [7,8].

Aβ peptides are most frequently measured in the cerebrospinal fluid (CSF) or through brain imaging of Aβ deposition with positron emission tomography (Aβ-PET). Both biomarkers have demonstrated high diagnostic and prognostic value [9–12], and they might start changing decades before the clinical onset of AD [8,13,14]. However, despite the robustness of these biomarkers, they are not suitable for a broad screening of the population, either because of invasiveness or high cost and low availability of the technology in primary care clinical settings. Given the greater accessibility of blood sampling, there is considerable interest in examining whether circulating Aβ levels correlate with brain Aβ levels and, therefore, with risk of developing AD dementia. A blood-based biomarker would be a less invasive and cost-effective screening method to identify individuals at-risk who could be subsequently confirmed by neuroimaging or CSF analysis. In this context, several large studies have consistently reported that a lower Aβ42/Aβ40 ratio in plasma is associated with higher risk of dementia [15–19], and greater cognitive decline in healthy control subjects at follow-up [20]. Nevertheless, some studies have reported weak or no association of the Aβ42/Aβ40 plasma ratio with AD [21–23].

Some of these contradictory findings likely reflect the complexity of measuring Aβ in plasma and the preanalytical and analytical differences between quantitative methods [24,25]. Differences in study populations with regard to factors such as age or disease stage [26] are also confounding factors. Moreover, to date, assessment of the accuracy of blood Aβ biomarkers relies essentially on the use of clinical diagnosis as the gold standard, despite the fact that it has shown sensitivities ranging from 70.9% to 87.3%, and specificities from 44.3 to 70.8 [27], which could seriously skew the results of any test and is almost certainly a relevant source of variability between studies.

The aim of this study was to examine the potential of the plasma Aβ42/Aβ40 ratio as a marker of cortical Aβ deposition and its use as a screening tool for clinical trial enrichment of cognitively normal (CN) subjects with high brain Aβ levels. With this in mind, we focused on the CN group of the Australian Imaging, Biomarker and Lifestyle Flagship (AIBL) Study using Aβ-PET as the gold standard, supported by previous results showing an association between Aβ42/Aβ40 plasma ratio and brain Aβ levels [28–31]. Moreover, we have taken a comprehensive approach for the evaluation of Aβ42/40 plasma ratio, differentiating the peptide fractions that are found free in plasma (FP42/40) from the total Aβ peptides in plasma (TP42/40) and the amount of Aβ that is bound to other plasma components (BP42/40), by means of validated enzyme-linked immunosorbent assays (ELISAs) [32]. In this study, the cross-sectional and longitudinal association of these plasma markers with brain Aβ-PET results was evaluated, together with an assessment of their diagnostic performance and ability to predict brain Aβ deposition trajectories, evaluating the potential of plasma Aβ ratios as enrichment tools for secondary prevention clinical trials.

2. Methods

2.1. Study population

CN subjects from the AIBL cohort included in this study were selected from those who underwent Aβ imaging with PET. Complete description of the clinical classification procedures in this study was described previously [33]. Subjects were followed-up for 72 months with visits at baseline (bl) and 18-month intervals (visits m18, m36, m54, and m72).

2.2. Amyloid PET imaging

At each of these time points, cortical Aβ burden was assessed using PET with either ^{11}C-Pittsburgh Compound-B (PiB) or ^{18}F-flutemetamol. The PET methodology for each tracer has been previously described [34,35] (see Supplementary material, Imaging Methods for detailed description). To use the results of both PET tracers as a single continuous variable, flutemetamol results were transformed into PiB-like standardized uptake value ratios (SUVR) termed BeCKeT [36]. The SUVR/BeCKeT was then dichotomized into high (Aβ+) or low (Aβ−) Aβ burden using a cutoff value of 1.5 [36].

Those individuals with both a valid Aβ-PET measurement and a valid corresponding plasma measurement at visits m18, m36, and/or m54 were considered in the cross-sectional and in the discriminating performance analysis. For longitudinal analysis, subjects with both valid plasma and Aβ-PET data at bl and at least a valid Aβ-PET measurement during the whole follow-up were considered.

2.3. Plasma Aβ40 and Aβ42 quantification

Plasma samples were obtained using ethylenediaminetetraacetic acid (EDTA) as anticoagulant and following AIBL procedures [30], and were conserved at −70°C until analysis without undergoing any extra freezing/thaw cycles. Only plasma samples from visits m18, m36, and m54 were available for Aβ plasma analysis in this study. Aβ40 and Aβ42 peptides were quantified using ABtest40 and ABtest42, respectively (Araclon Biotech Ltd. Zaragoza, Spain), being blinded to all participant characteristics at the time of

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