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Longitudinal plasma amyloid beta as a biomarker of Alzheimer's disease

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Abstract

Alzheimer's disease (AD) affects more than twenty-five million people worldwide and is the most common form of dementia. Symptomatic treatments have been developed, but effective intervention to alter disease progression is needed. Targets have been identified for disease-modifying drugs, but the results of clinical trials have been disappointing. Peripheral biomarkers of disease state may improve clinical trial design and analysis, increasing the likelihood of successful drug development. Amyloid-related measures, presumably reflecting principal pathology of AD, are among the leading cerebrospinal fluid and neuroimaging biomarkers, and measurement of plasma levels of amyloid peptides has been the focus of much investigation. In this review, we discuss recent data on plasma β -amyloid ($A\beta$) and examine the issues that have arisen in establishing it as a reliable biomarker of AD.

Keywords

Alzheimer's disease; Protein biomarker; Plasma amyloid

Plasma A β as a biomarker: overview

β -Amyloid (A β) is a 38- to 43-amino-acid peptide produced by proteolytic cleavage of amyloid precursor protein (APP). In the AD brain, A β accumulation is considered to play a pivotal role in neuronal loss and cognitive impairment (Selkoe 1994). Although APP exists throughout the body (Arai et al. 1991), A β is primarily produced in brain (Laird et al. 2005), making cerebrospinal fluid (CSF) an obvious candidate for A β detection. Levels of CSF A β 42 decline with AD progression, which may suggest neuronal loss and increasing A β plaque development (Jensen et al. 1999; Andreasen and Blennow 2002).

Given the somewhat invasive nature of CSF sampling, changes in A β in plasma would be an attractive biomarker. As reviewed in detail recently (Hampel et al. 2011), changes in CSF and plasma A β may reflect a shift from soluble A β species in the periphery with increased insoluble A β plaque formation in the brain. In subjects with familial AD or Down syndrome (DS), plasma A β rises sharply before dementia onset, perhaps reflecting increased A β production (Scheuner et al. 1996; Tokuda et al. 1997; Yonkin 1998; Ertekin-Taner et al. 2000, 2008; Coppus et al. 2011). In the case of DS, recent studies suggest that plasma A β is less of a predictor of dementia, per se, but can predict cognitive function in adults with DS independently (Head et al. 2011). Data from our group demonstrate that ratio of A β 42:40 rather than absolute levels of the peptides is important to the pathophysiology of AD in genetically susceptible populations (Matsuoka et al. 2009). More recently, in an Alzheimer's disease neuroimaging initiative (ADNI) study (Toledo et al. 2011b), we analyzed data from 715 ADNI subjects with baseline A β 40 and A β 42 plasma measurements (50% with 4 serial annual measurements) including: 205 cognitively normal controls (CN), 348 patients mild cognitive impairment (MCI) and 162 with AD ($n = 162$). We also integrated these analyses with all available ADNI data on PIB PET, MRI and tau, and A β 42 measures in cerebrospinal fluid (CSF) on these subjects. We noted that the effect of age differed according to AD stage and that plasma A β 42 showed a mild correlation with other biomarkers of A β pathology, but they also were associated with infarctions in MRI. However, longitudinal measurements of A β 40 and A β 42 plasma levels showed only modest value as a prognostic factor for clinical progression. Thus, these findings show that plasma A β measurements have limited value for disease classification and modest value as prognostic factors over the 3-year follow-up period in this ADNI study. However, with longer follow-up, plasma A β measurements within subjects could be developed into a minimally invasive screen to identify those at increased risk for AD. However, there is clearly a need for further research into the biology and dynamics of A β , as discussed below. There is also a need for longer term studies to determine the clinical utility of measuring plasma A β . Data collected thus far on plasma A β in sporadic, familial AD and Down Syndrome are summarized in Table 1.

Sources of plasma A β

APP has been localized in several peripheral tissues and organs that express β -secretase (Arai et al. 1991; Sinha et al. 1999; Vassar et al. 1999). Although these tissues are viable sources to plasma A β , their contribution is likely to be nominal given the vastly greater amount of A β produced in the brain (DeMattos et al. 2002; Cirrito and Holtzman 2003).

Furthermore, data suggest that A β in brain can be cleared into the periphery through rapid receptor-mediated transport across the blood–brain barrier (Shibata et al. 2000; DeMattos et al. 2002; Deane et al. 2003, 2004a, 2004b). Increased levels of plasma A β have been reported in AD mouse models (Kawarabayashi et al. 2001) or after treatment with binding agents (DeMattos et al. 2002; Deane et al. 2003; Matsuoka et al. 2003). In AD patients, plasma A β levels are elevated and mainly incorporated into lipo-proteins and different plasma proteins (Biere et al. 1996).

Variables that affect plasma A β

In comparison to CSF, validation of plasma A β as a predictor of dementia in sporadic or late-onset forms of AD has been more difficult to determine. Relationships have been found between plasma A β 40:42 to A β 42:40 and dementia, but the direction of these associations vary among studies (Fukumoto et al. 2003; Mayeux et al. 2003; Blasko et al. 2008; Lopez et al. 2008; Schupf et al. 2008; Toledo et al. 2011b). More consistency has been found in the ratio of plasma A β 42:40, with non-demented patients usually having higher risk of AD with lower A β 42:40 ratios (Graff-Radford et al. 2007; Okereke et al. 2009). In terms of predicting whether patients with MCI will convert to AD, no consistent change in plasma A β or ratio has been found (Fukumoto et al. 2003; Lopez et al. 2008; Toledo et al. 2011b). However, studies demonstrate that age-related changes (increases) in plasma A β and reduced A β 40:42 ratio are primarily restricted to MCI patients or individuals with worsening cognitive status (Toledo et al. 2011b).

Sources of variability in findings from existing studies are potentially due to variability in subject age and/or with disease severity (Fukumoto et al. 2003; Giedraitis et al. 2007), but may also relate to study size; very few large-scale studies have been attempted. A recently published study in a large cohort of elderly patients identified an association between low cognitive reserve and plasma A β 42:40, which accentuated the relationship between low plasma A β 42:40 and greater cognitive decline in non-demented participants (Yaffe et al. 2011). Below we discuss potential factors that may contribute to the variability seen in studies and what steps are still needed to identify the parameters for clinical utility of plasma A β .

Impact of age on plasma A β

Several studies suggest that the levels of A β in plasma increase as a function of age in non-demented individuals (Matsubara et al. 1999; Fukumoto et al. 2003; Mayeux et al. 2003). Although the mechanisms underlying this change are not confirmed, data from rodent studies implicate age-related reduction hepatic clearance of A β , due to alterations in low-density lipoprotein receptor-related protein 1 (LRP-1) (Tamaki et al. 2006). Studies in humans implicate the renal system and have found strong relationships between plasma A β and creatinine (Cr) levels (Arvanitakis et al. 2002).

Concurrent disease states

To different degrees, aged populations are characterized by multiple health concerns. Although the etiology of AD has not been demonstrated to be vascular origin, plasma A β

level changes have been linked to neurovascular disease. A growing body of evidence suggests an association between vascular risk factors and AD, with neurovascular disease hypothesized to be an exacerbating factor of AD neuropathology (Girouard and Iadecola 2006). Indeed, in another recent ADNI study (Toledo et al. 2011a), we examined the relationship between vascular risk factors (VRF) and A β brain burden measured by Pittsburgh Compound B (PIB) PET studies. Briefly, 99 subjects had a PIB PET study and had information available on VRF (body mass index, systolic and diastolic blood pressure, cholesterol and fasting glucose) in the ADNI cohort, while 81 subjects also had plasma cortisol, brain natriuretic peptide, leptin, c-reactive protein and superoxide dismutase-1 measurements. All subjects also had APOE genotyping. We used these data in a regression stepwise model to assess the relation between the VRF and the composite PIB PET score. The final model included baseline age, clinical diagnosis, number of APO ϵ 4 alleles, body mass index (BMI) and diastolic blood pressure (DBP) as variables. BMI showed an inverse relation with PIB PET score, and DBP had a positive relation with PIB PET score. In a second adjusted model, plasma cortisol levels also were associated with PIB PET score, but there was no association of systolic blood pressure, cholesterol, or impaired fasting glucose with PIB PET values. Thus, based on these data there appears to be an association between PIB PET measures and DBP as well as cortisol, thereby suggesting a possible link between these two VRF and deposits of A β in brain. In terms of plasma A β , although longitudinal studies are needed to confirm, current data suggest that subjects with AD, MCI, cerebral amyloid angiopathy, or ischemia, levels of plasma A β 40 may be a viable biomarker of cerebrovascular damage (Lee et al. 2005; Gurol et al. 2006).

In addition to vascular conditions, studies have focused on how plasma A β levels can be influenced by known covariates of AD, such as clearance of Cr. As both Cr and A β are cleared through the kidney, elevated levels of Cr are considered indicative of renal insufficiency. Indeed, data suggest direct relationships between renal function and plasma A β (Arvanitakis et al. 2002). Another important covariate of AD that may influence plasma A β levels is homocysteine, whose levels have been correlated with cognitive decline in AD and conversion of MCI to AD (Tucker et al. 2005; Blasko et al. 2008).

Methodological concerns

Compared to CSF A β levels, the levels of plasma A β 42 are very low, which has complicated studies due to the propensity for subjects to fall below the linear range of detection on many platforms. Levels of A β 40 in plasma are much higher, but data are still mixed regarding the direction of change with advancing disease. A potential factor in this variability may lie with the variety of ELISA and fluorometric bioassay platforms available. Sensitivity and specificity of the platforms used are highly reliant on the antibodies used, which can vary. There are also several ELISA systems and protocols that have been used in clinical studies, which make data comparison difficult. Interestingly, recent studies investigating multiple assay protocols for plasma A β in different laboratories found very good reproducibility of values (Okereke et al. 2009). While this has not necessarily been the case for CSF measures (Mattsson et al. 2011), a recent ADNI round-robin study of CSF tau and A β showed very good inter-lab reproducibility (Shaw et al. 2011).

In addition to issues arising as a result of assays, A β in both CSF and plasma is typically complexed to a variety of binding proteins, which may complicate detection (Biere et al. 1996; Koudinov et al. 1998). For example, A β is hydrophobic and binds to certain test tube walls as well as to several plasma proteins, including albumin and low-density lipoprotein receptor-related protein-1 (Matsubara et al. 1999; Hampel et al. 2011). Further, since measurement of soluble A β is done with assays that are independent of aggregation state, both plasma protein binding and oligomerisation could mask the detection of A β in plasma or CSF measured by these assays, which may explain contradictory results.

Variability in samples is also an issue, with reports suggesting that fluctuations of A β levels in CSF are dependent on the time of day and subject activity level (Bateman et al. 2007). Whether this is the case for plasma A β has yet to be conclusively determined. Data from AD rodent models are in concert with that seen in humans, with A β in brain being acutely impacted by environmental stimuli could significantly affect brain A β level (Kang et al. 2007). Other data from animal models suggest that time after eating can significantly affect plasma A β level. Recent data suggest that plasma A β in a fed state was significantly higher than that in a fasted state (Takeda et al. 2009).

Conclusions

Though controversy remains, there is a consensus that a pivotal and presumably initiating process in sporadic and genetically determined AD is the accumulation of toxic A β species in brain. Biomarkers reflecting this accumulation are thus likely to be important in the selection of individuals for AD prevention and treatment trials and monitoring the effects of anti-amyloid interventions. Indeed, among the most exciting developments in AD therapeutic research is the development of amyloid PET imaging and CSF A β ₄₂ measurement as indicators of brain amyloid. If anti-A β therapies become available, it is likely that treatment will be guided by biomarkers of brain A β .

Unfortunately, amyloid PET scanning is expensive and not yet generally available, and lumbar puncture is somewhat invasive. A peripheral blood biomarker would offer substantial advantages over these approaches, allowing readily acceptable screening and monitoring. While it is known that there is communication between the peripheral and central A β pools (via receptor mediated as well as passive mechanisms), the utility of plasma A β measurements has remained limited. While some studies have shown correlations between plasma A β and dementia risk and/or progression, such findings have been inconsistent. Biological and methodological issues likely contribute to these limitations, thereby underlining the need for a better understanding of the biology and dynamics of plasma A β as well as the need for longer term studies to determine the clinical utility of measuring plasma A β .

As discussed, plasma A β increases sharply before dementia onset, perhaps reflecting increased A β production in subjects with familial AD or Down syndrome (Scheuner et al. 1996; Tokuda et al. 1997; Ertekin-Taner et al. 2008). The same has not been found in sporadic or late-onset forms of AD. Although relationships have been found with plasma A β ₄₀ or 42 and dementia, the direction of these associations is variable. A recent study of

plasma A β 42 in normal, mildly impaired, and mildly demented cohorts is discouraging and yet provides some reason for optimism (Toledo et al. 2011b). Overall, plasma A β measurements were not useful in distinguishing among the cohorts, and showed minimal association with disease progression. At present, this study and that reported previously support the idea that plasma A β assays are not useful for diagnosis or prediction of decline. However, a significant association between plasma A β 42 and brain amyloid was found, as indicated by CSF A β 42, while the ADNI study reported mild correlation of plasma A β 42 and other biomarkers of A β pathology, but they also were associated with infarcts detected by MRI (Toledo et al. 2011b).

As we discuss, sources of variability in plasma A β studies may be due to difficulty in consistency of subject age, disease severity. Recent data also suggest that technical precision may also be involved. Using a robotized method for specific steps allowed for a large improvement in consistency over results reported in the literature, and several significant relationships between plasma and CSF biomarkers were found (Figurski et al. 2012). Although these correlations are still not strong enough to support use of plasma A β as a diagnostic screening test, the data suggest that plasma A β 42 is well suited for use as a pharmacodynamic marker.

As opposed to studies examining levels of peptide alone, reports on ratio of plasma plasma A β 42:40, have had more consistent results, with lower A β 42:40 ratios predicting higher risk of AD (Graff-Radford et al. 2007; Okereke et al. 2009). Furthermore, a large cohort study of elderly patients found that low cognitive reserve and plasma A β 42:40, which accentuated the relationship between low plasma A β 42:40 and greater cognitive decline in non-demented participants (Yaffe et al. 2011).

With improvements of assay conditions (e.g., with increasing sensitivity and reproducibility, and standardization of specimen handling to minimize interactions with other blood constituents and collection materials), and if the confounding effects of factors such as age and renal function are fully considered, it may be reasonable to expect that such measurements may become useful biomarkers of brain amyloidosis. This, in turn, could greatly facilitate the development and clinical application of disease-modifying therapies for AD. Improvements in the reproducibility of plasma A β 42 and A β 40 measurement support the utility of this biomarker test as a pharmacodynamic marker that reflects drug effect on A β processing.

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Table 1

Reported changes in plasma amyloid as a function of age, disease and Down Syndrome

References	Setting	Cohort and outcome	Main finding: cross sectional	Main finding: longitudinal change
Scheuner et al. (1996)	Cohort study	Familial or sporadic AD and age matched controls	Increase in A β 42 in familial AD	Not examined
Tokuda et al. (1997)	Cohort study	Down syndrome (age 19–61) and aged matched normal controls	Increase in A β 40 and A β 42 in DS compared to controls	Not examined
Younkin (1998)	Cohort study	Elderly patients with sporadic AD and control matched	A β 42 increase in plasma of subjects with mutated gene causing early onset familial AD	Elevated A β 42 in subjects with FAD-linked mutations in not a secondary effects of AD state
Mayeux et al. (1999)	Population-based study	Normal elderly development of AD	High baseline A β 42 and A β 40 in incident AD	No change in incipient AD. Only baseline A β 42 significant after the statistical adjustments
Ertekin-Taner et al. (2000)	Cohort study	First-degree relatives of patients with typical late-onset AD (LOAD) and AD patients	A β 42 increase in first-degree relatives of patients with typical late-onset AD (LOAD) and early AD	Identification of a novel LOAD locus on chromosome 10 that acts to increase A β
Fukumoto et al. (2003)	Cohort study	AD, MCI, and Parkinson patients, and control	Plasma A β measures increase with age	Plasma A β measures are unspecific for the clinical diagnosis of MCI or sporadic AD
Mayeux et al. (2003)	Population-based study	Normal elderly and MCI—development of AD	High baseline A β 42 in incident AD	Longitudinal decline in A β 42 in incipient AD
Gurol et al. (2006)	Cohort study	Subjects with AD or AD/MCI and an subjects with cerebral amyloid angiopathy (CAA)	Plasma A β 40 concentration is independently associated with extent of white matter hyperintensity in subjects with AD, MCI, or CCA	Circulating A β 40 peptide is a novel biomarker in AD, MCI, and CCA
Van Oijen et al. (2006)	Population-based study	Normal elderly development of AD	High baseline A β 40, but not A β 42, in incident AD	Not examined
Graff-Radford et al. (2007)	Cohort study, primary care	Normal elderly development of MCI or AD	Low baseline A β 42/A β 40 ratio in incident MCI and AD	Not examined
Giedraitis et al. (2007)	Cohort study	Control, MCI, and AD	Relationship between CSF and plasma A β in control but not between MCI and AD. No different in plasma A β between diagnostic groups	Not examined
Blasko et al. (2008)	Community-based cohort study	Normal elderly development of MCI or AD	No change in baseline A β 42 in incident AD	Longitudinal increase in A β 42 in incipient MCI and AD
Lopez et al. (2008)	Population-based study	Healthy elderly and MCI development of AD	High baseline A β 42 and A β 40 in incident AD	Longitudinal increase in A β 42 and A β 40 in independently of cognitive change

References	Setting	Cohort and outcome	Main finding: cross sectional	Main finding: longitudinal change
Schupf et al. (2008)	Cohort study of Medicare recipients,	Normal elderly development of AD	High baseline A β 42 (but not A β 40) in incident AD	Longitudinal decrease in A β 42 (but not A β 40) in incident AD
Ertekin-Taner et al. (2008)	Cohort study	First-degree relatives of AD patients and controls	Plasma A β is significantly elevated in the LOAD first-degree relatives in comparison to unrelated controls	Changes are not due to ApoE4 or pathogenic coding mutations
Sundelof et al. (2008)	Population-based study	Normal elderly development of AD	Low baseline A β 40 (but not A β 42) in incident AD at age 77	No longitudinal change in A β 42 or A β 40 in incident AD. No change in A β 40 or A β 42 in prodromal AD at age 70
Okereke et al. (2009)	Population-based study	Female registered nurses age 30–55 followed up into late life	Increase in A β 40:42 ratios since midlife predicted greater decline in the global score. No association of cognitive decline with midlife plasma A β 42 levels alone or with change in A β 42 levels since midlife	Higher A β 40/A β 42 ratio in midlife and increase of A β 40/A β 42 ratio in late life predict cognitive decline
Roher et al. (2009)	Longitudinal case–control study	AD and non-demented controls	No change in A β 42 or A β 40	No disease-associated change over time
Matsuoka et al. (2009)	Cohort	DS patients with dementia	Ratio of A β 42:A β 40 was associated with the presence of dementia which persisted after adjustment for age, sex level of mental retardation, and apolipoprotein E genotype	Not examined
Hansson et al. (2009)	Cohort study, memory clinic	MCI development of AD	No change in A β 42 or A β 40	Not examined
Hampel et al. (2011)	Review	Normal elderly and MCI development of AD	Contradictory finding are due to analytic difficulties	Not examined
Head et al. (2011)	Cohort study	Non-demented adults with DS, young and old individuals without DS and patients with AD	In demented DS adults, ApoE4 was associated with higher A β 40 but not A β 42. Improved prediction of neuropsychological scores by plasma A β . After controlling for level of intellectual disability (mild, moderate, severe) and the presence or absence of dementia	Not examined
Coppus et al. (2011)	Population-based study	Down Syndrome have a significantly higher plasma A β 1–40 concentration than the non-demented	Increase in plasma A β at dementia onset in Down's Syndrome. The risk to develop dementia increased to 2.56 for A β 1–42	Not examined
Toledo et al. (2011a, b)	Longitudinal case, Cohort study	Normal elderly and MCI development of AD	Plasma A β 42 showed mild correlation with other biomarkers of A β pathology and were associated with infarctions in MRI	Longitudinal increase in A β 42 and A β 40
Toledo et al. (2011a, b)	Population-based study	Normal elderly and MCI development of AD	Association between A β brain burden and diastolic blood pressure and cortisol	Possible link between these cardiovascular risk factors and A β burden