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REVIEW

Plasma amyloid beta measurements - a desired but elusive Alzheimer´s disease biomarker

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Abstract

Cerebrospinal fluid and positron emission tomography biomarkers accurately predict an underlying Alzheimer's disease (AD) pathology; however, they represent either invasive or expensive diagnostic tools. Therefore, a blood-based biomarker like plasma amyloid beta (Aβ) that could correlate with the underlying AD pathology and serve as a prognostic biomarker or an AD screening strategy is urgently needed as a cost-effective and non-invasive diagnostic tool. In this paper we review the demographic, biologic, genetic and technical aspects that affect plasma Aβ levels. Findings of cross-sectional and longitudinal studies of plasma Aβ, including autosomal dominant AD cases, sporadic AD cases, Down syndrome cases and population studies, are also discussed. Finally, we review the association between cerebrovascular disease and Aβ plasma levels and the responses observed in clinical trials. Based on our review of the current literature on plasma Aβ, we conclude that further clinical research and assay development are needed before measures of plasma Aβ can be interpreted so they can be applied as trait, risk or state biomarkers for AD.

Introduction

Alzheimer's disease (AD) is the most common underlying cause of dementia globally, and the leading cause of years lost to disability in high-income countries as well as the second greatest cause of this worldwide according to the World Health Organization. A definite diagnosis of AD can only be established by postmortem studies that demonstrate the presence of extracellular amyloid plaques and intracellular tau neurofibrillary tangles [1]. The measurement of the neuropathologic hallmarks of AD, namely tau and amyloid beta (Aβ), in cerebrospinal fluid (CSF) has been shown to be a reliable diagnostic biomarker for AD [2], but it would be attractive to have less invasive AD biomarkers, such as those that can be measured in plasma. Positron emission tomography (PET) using florbetapir-F18 (AV-45) or Pittsburgh Compound-B-C11 (PiB) as radiotracers reflects fibrillar brain amyloid deposits and is deemed a reliable method to measure brain amyloid plaque burden [3,4], but cost and availability of PET biomarker measures are drawbacks associated with this diagnostic strategy. Therefore, the measurement of Aβ in plasma would be the least invasive and most cost-effective biomarker assay. In addition, blood samples could readily be obtained in non-specialized facilities and sent to specialized laboratories to conduct the measurements. However, published results on the correlation of plasma Aβ with the presence of AD are contradictory and plasma Aβ measurements are subject to more sources of variability than CSF Aβ measurements [5]. Below we will summarize the demographic, biological and technical aspects related to Aβ plasma measures, the results of cross-sectional and longitudinal studies in populations with sporadic AD and AD due to autosomal dominant genetic inheritance, and application of these measurements in clinical trials.

Aβ distribution in blood, CSF and brain

Aβ production and correlation between plasma, CSF and parenchymal Aβ measurements

Aβ is a byproduct of Aβ precursor protein (APP) metabolism that is generated by nearly all cells, and amyloid plaques are the result of the deposition of mainly $Aβ_{1-40}$ and $Aβ_{1-42}$ in the brain, although other species of Aβ are also present [6]. The mechanism leading to Aβ deposition differs in subjects for whom this occurs on a genetic basis, leading to familial AD (FAD), versus those who develop sporadic AD. In autosomal dominantly inherited forms of AD, the main mechanism is an increased production of Aβ species [7], while the consensus is that there is a decreased Aβ clearance in sporadic forms of

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AD, which is modulated by the apolipoprotein E (APOE) genotype [8,9].

The blood-brain barrier and the blood-CSF barrier regulate the passage of solutes between blood and the central nervous system (CNS), including Aβ. Although there are a number of receptors that are implicated in the influx (for example, receptor of advanced glycation end products) and efflux (for example, low-density lipoprotein receptor, low-density lipoprotein receptor-related protein 1 and 2, P-glycoprotein, low-density and very low-density lipoprotein receptor) of Aβ through the blood-brain barrier, most of the studies that compared plasma Aβ levels with their CSF counterparts [10-13] or the binding of PET Aβ radiotracers [10,14] have found no or low correlations between Aβ plasma measurements and CSF Aβ and PET amyloid plaque measurements. On the other hand, CSF and PET values show a high inverse correlation [10,15,16], although CSF ELISA/Luminex assays measure soluble Aβ and PIB/AV-45 PET measure insoluble fibrillar Aβ deposition. However, one study has described a stronger correlation between plasma Aβ and PET PiB measurements [17].

Origin, distribution and clearance of Aβ in plasma

There are several factors that can explain the low correlation between plasma and CSF Aβ/PET amyloid plaque measurements. First, Aβ species in the CSF and the CNS interstitial fluid originate in the CNS. CNS Aβ is then thought to diffuse from interstitial fluid into the CSF, while passage of Aβ through the blood-brain barrier is limited. In addition, Aβ in plasma and blood does not originate only in the brain since it also is the product of APP metabolism in skeletal muscle, pancreas, kidney, liver, vascular walls, lung, intestine, skin and several glands and APP can be found in almost all peripheral cells [18-20]. In addition, most of the $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ in plasma are bound to several proteins (that is, apolipoprotein A-I, A-IV, E and J, α2-macroglobulin, complement factors, immunoglobulins, transthyretin, apoferritin and serum amyloid P component) and erythrocytes [19,21]. Finally, platelets are another important source of $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ in plasma [19] and activated platelets release APP and Aβ [22]. Therefore, it is not surprising that Aβ plasma values may only partially reflect altered APP metabolism or Aβ in the CNS since there is no evidence that AD is a systemic Aβ amyloidosis. While correlations between undiluted, diluted and cell bound plasma samples have been reported by some investigators to be high, the diagnostic utility of measuring Aβ at different dilutions or in different fractions remains uncertain [23]. Finally, regarding the elimination of plasma Aβ, animal models have implicated the liver as the major organ responsible for the clearance of Aβ from plasma [24], followed by renal clearance [25].

Demographic, clinical, genetic and technical issues affecting Aβ levels and measurements

Demographic, genetic diagnostic and assay related factors affecting Aβ plasma levels

Most studies have described a strong association between older age and higher levels of plasma Aβ [10,26-31]. This association has not been established in Down syndrome (DS) subjects, and there are conflicting results, with some studies finding an association [32,33] and others not [34,35]. Two studies have evaluated the heritability of Aβ plasma levels. The paper by Ertekin-Taner *et al.* found a higher heritability (54% for $A\beta_{1\text{-}40}$ and 73% for $A\beta_{1\text{-}42}$) [36] than the one by Ibrahim-Verbaas *et al.* (23% for $A\beta_{1\text{-}40}$ and 30% for $A\beta_{1\text{-}42}$) [37]. None of the studies found that APOE genotype explained a significant amount of the heritability, but the study by Ibrahim-Verbaas *et al.* found an association between SNPs located at the presenilin 2 gene (*PSEN2*) and $A\beta_{1\text{-}40}$ levels. However, some studies have reported an association of lower $A\beta_{1\text{-}42}$ in the presence of APOE ε4 alleles [10,28,38] and at least one study has described a lower $A\beta_{1\text{-}42}/A\beta_{1\text{-}40}$ ratio in non-APOE ε4 subjects in the highest tertile of physical activity [39]. A third study found increased Aβ in young, non-demented first-degree relatives of late onset AD compared to unrelated controls [31]. Other factors associated with Aβ plasma levels are creatinine levels [10,28,38,40], high density lipoproteins [27], body mass index [27], race [38] and sex [38,41]. One study included age, platelet count, total protein concentration and creatinine levels in a multivariate analysis and found that these variables accounted for 12.9% of plasma levels, underscoring the importance of using multivariable models that adjust for possible confounders [10]. Like CSF levels, plasma levels show a circadian fluctuation that decreases with aging [11]. Therefore, standardization of sampling time is important.

Technical aspects regarding sample storage and Aβ plasma measurements

$A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ are stable at 2 to 8°C for 6 h but when Aβ is kept at room temperature for 24 h levels drop considerably, exceeding a 20% loss in most of the pools [42-45], although ratios of different Aβ species can be more stable [43]. Storage at -20°C is not suitable for long-term storage and Aβ levels are not stable through freeze-thaw cycles following storage at -20°C, whereas storage at -70°C shows no reductions in Aβ levels for up to three cycles and Aβ levels are stable for at least 12 months when stored at this temperature [42,45]. One study has reported that some Aβ peptides increase their concentration once frozen [46]. Repeated samples taken during fasting and in the post-prandial state and repeated samples taken from cognitively normal (CN) subjects within three weeks show coefficients of variation (CV)

that are within the range of the variability of the assay in both cases, indicating that these pre-analytical factors do not have an important effect on Aβ measurements [13]. Although not formally tested in plasma, storage in polypropylene tubes currently is the best way to minimize adherence of Aβ to the wall of storage vials compared to polystyrene for CSF samples [47], and is current practice for plasma samples. Different types of polypropylene are used in the manufacture of biofluid storage vials, but the effects of these differences on Aβ levels following short- and long-term storage are not well documented. Finally, collection parameters like collected blood volume and time to freeze have been associated with levels of plasma Aβ [48] and Aβ levels in serum are also less stable than plasma Aβ levels [43].

Association of Aβ with AD and cerebrovascular disease

Cross-sectional and longitudinal results in DS individuals and subjects harboring autosomal dominant FAD mutations

The initial study by Scheuner *et al.* described increased plasma levels of $A\beta_{1-42}$ in subjects from FAD kindreds with pathogenic mutations in the *APP*, *PSEN1* and *PSEN2* genes when compared to non-mutation bearing controls [49] and Kosaka *et al.* found increased plasma levels of $A\beta_{1-42}$ when comparing AD patients carrying the βAPP717 mutation to sporadic AD patients [50]. Recently, a cross-sectional cohort of asymptomatic carriers of the PSEN1 E280A mutation had higher $A\beta_{1-42}$ and $A\beta_{1-42}$/$A\beta_{1-40}$ than matched CN controls without the mutation [51].

DS subjects show higher plasma $A\beta_{1-42}$ and $A\beta_{1-40}$ levels than CN subjects without trisomy 21 [34,52]. Two studies found no differences comparing DS with and without dementia, although an association between Aβ levels and neuropsychological scores in multivariable adjusted models was found [34,35]. In one of these studies demented DS (dDS) subjects with longer dementia duration showed higher $A\beta_{1-42}$, lower $A\beta_{1-40}$ and a higher $A\beta_{1-42}/A\beta_{1-40}$ ratio than those with shorter dementia duration [35]. Two other studies comparing dDS to cognitively normal DS (cnDS) found a higher $A\beta_{1-42}$/$A\beta_{1-40}$ ratio in dDS [53] and increased $A\beta_{1-40}$ levels in dDS subjects compared to cnDS that remained stable during a follow-up of several years [54]. Consecutive studies by Schupf *et al.* [32,52] have described increased $A\beta_{1-42}$ in dDS when compared to cnDS. These and other studies of plasma Aβ levels in subjects with trisomy 21 and pathogenic FAD mutations are summarized in Table 1.

There are limited data from prospective studies of plasma Aβ levels in subjects with DS (Table 2), but one study described an increased risk of dementia in subjects who at baseline had increased levels of $A\beta_{1-42}$ or $A\beta_{1-40}$ [54]. However, in studies conducted by another group, only baseline levels of $A\beta_{1-42}$ were associated with an increased risk of dementia and death [32]. Finally, in a third study, Schupf *et al.* [33] compared the measurements of the last and baseline visits, finding an increased risk of dementia with an increase in $A\beta_{1-40}$, a decrease in $A\beta_{1-42}$ or a decrease in $A\beta_{1-42}/A\beta_{1-40}$ ratio with repeated sampling during follow-up.

Cross-sectional results in sporadic AD cases

Results differ between studies including CN and sporadic AD subjects (Table 3). Different associations have been reported, with increased levels of $A\beta_{1-42}$ in AD patients [27], decreased levels of $A\beta_{1-42}$ in AD [14] and increased $A\beta_{1-40}$ in AD [55]. Regarding the gender effect, one study found higher $A\beta_{1-42}$ levels in women with mild cognitive impairment (MCI) compared to CN women and CN and MCI male subjects [41].

Some studies classified subjects not only based on clinical diagnosis but also on AD-like CSF profiles for tau and Aβ profiles [10,13,56]. In a study that included CN and MCI subjects, the group of CN and MCI subjects with AD-like CSF tau and Aβ profiles showed lower plasma $A\beta_{1-42}/A\beta_{1-40}$ than CN and MCI subjects with normal CSF tau and Aβ levels [13]. Another study found decreased $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$ in MCI and AD subjects with an AD-like CSF tau and Aβ signature when compared to MCI and AD subjects with normal CSF tau and Aβ levels [56]. A more complex association was found for plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ levels in the AD Neuroimaging Initiative (ADNI) cohort, showing an interaction between age and diagnostic groups defined by an AD-like CSF tau and Aβ profile [10]. Based on these results, only younger MCI and AD subjects with an AD-like CSF signature showed lower $A\beta_{1-40}$ and $A\beta_{1-42}$ values than older MCI and AD subjects with an AD-like CSF signature or subjects with a normal CSF signature. These findings indicate that the presence of AD-like CSF in younger cognitively impaired subjects was what defined the group with lower plasma Aβ. There were not enough CN subjects with AD-like CSF to test the association in this group of subjects who are in the pre-symptomatic stage of AD. Although most of these studies do not report sensitivity, specificity or area under the curve (AUC) measures for plasma Aβ levels, it is clear from these publications that determination of plasma Aβ levels is not useful as a diagnostic classifier.

Longitudinal results in the CN population and MCI and sporadic AD cases

Different measures of plasma Aβ have been associated with progression to dementia (Table 4): high baseline $A\beta_{1-42}$ [30,57], low baseline $A\beta_{1-42}/A\beta_{1-40}$ [58,59], low baseline $A\beta_{1-40}$ or $A\beta_{1-42}$ [60], high baseline $A\beta_{1-40}$ [29], high $A\beta_{1-40}$ or low $A\beta_{1-42}/A\beta_{1-40}$ [61] and low $A\beta_{1-40}$ in older

Table 1. Cross-sectional studies in populations including Down syndrome and familial Alzheimer's disease due to trisomy 21 or autosomal dominant mutations, respectively

Study	Subjects	Mean age (years)	Platform and antibodies	%CV	Values in DS patients compared to controls			Values in dDS compared to cnDS		
					$A\beta_{1-40}$	$A\beta_{1-42}$	$A\beta_{1-42}/A\beta_{1-40}$	$A\beta_{1-40}$	$A\beta_{1-42}$	$A\beta_{1-42}/A\beta_{1-40}$
Schupf *et al.* 2001 [52]	97 cnDS 11 dDS	51.9 56	ELISA 6E10 R182 R165	-	↑	↑	-	=	↑	-
Schupf *et al.* 2007 [32]			ELISA 6E10 R182 R165	-	-	-	-	=	↑	-
Matsuoka *et al.* 2009 [53]	148 cnDS 52 dDS	54.2 56.0	ELISA 82E1 1A10 1C3	<11.0%	-	-	-	=	=	↑
Prasher *et al.* 2010 [35]	83 cnDS 52dDS	49.0 56.8	ELISA 6E10 R182 R165	-	-	-	-	=	=	=[a]
Head *et al.* 2011 [34]	11 yCN 12 aCN 17 AD 43 cnDS 52 dDS	46.5 74.2 75.3 45 53.3	ELISA Wako	-	↑	↑	=	-	-	-
Coppus *et al.* 2012 [54]	62 dDS 264 cnDS	54 50.6	xMAP INNO-BIA	-	-	-	-	↑	=	=
Reiman *et al.* 2012 [51]	10 PSEN1+ CN 10 PSEN1- CN	23 24	xMAP INNO-BIA	-	-	-	-	-	-	-

[a]dDS who had a dementia history of 4 or more years had increased $A\beta_{1-42}/A\beta_{1-40}$ compared with dDS with a more recent diagnosis. aCN, aged cognitively normal controls; AD, Alzheimer's disease; CN, cognitively normal; cnDS, cognitively normal Down syndrome; CV, coefficient of variation; dDS, demented Down syndrome; DS, Down syndrome; yCN, young cognitively normal controls.

subjects [62]. Finally, other studies found no associations of plasma Aβ levels with progression to dementia [10,13,63]. A study including information on vascular risk factors in midlife and a long follow-up period after baseline plasma sampling found an increased risk of dementia in subjects with low $A\beta_{1-40}$ and $A\beta_{1-42}$ at baseline and there was an interaction between plasma Aβ levels and diastolic blood pressure that indicated a higher incidence of dementia in subjects with higher diastolic blood pressure and low plasma Aβ levels [60]. One study that compared Aβ plasma levels in CN and MCI subjects who remained cognitively stable or progressed to AD found no differences in these two different cohorts [13], but, as noted above, there were significant differences based on the CSF-defined groups.

Other studies measuring plasma Aβ levels included correlations of these values with cognitive measures instead of using a diagnosis as outcome. One study included 481 subjects with a long follow-up and repeated measurements, and it used repeated brief telephone interviews for determining the study outcome, and the authors reported greater cognitive decline in subjects with a low $A\beta_{1-42}/A\beta_{1-40}$ at baseline [64]. However, inter-assay CV was over 30% (repeated subject measurements were included in the same assay with CV <10%). A larger study of 997 CN subjects followed for 9 years also found a faster cognitive decline in subjects with a lower $A\beta_{1-42}/A\beta_{1-40}$ at baseline [65]. Cosentino *et al.* [66] followed 880 subjects for 4.5 years who were CN at baseline or had cognitive impairment that was not severe enough for a dementia diagnosis. In this study, subjects with higher baseline $A\beta_{1-40}$ and $A\beta_{1-42}$ and stable or decreasing $A\beta_{1-42}$ levels during follow-up had a faster rate of decline, whereas $A\beta_{1-42}/A\beta_{1-40}$ showed no such association. On the other hand, in another study by Locascio *et al.* [67], the rate of cognitive decline in 122 AD patients was determined in subjects followed for 4.2 years, and these authors described a faster decline in subjects with lower

Table 2. Longitudinal studies in populations including Down syndrome

Study	Subjects	Mean age (years)	Follow-up duration	Platform and antibodies	CV	Analyte associated with conversion risk	Magnitude
Schupf *et al*. 2007 [32]	44 DSp 130 cnDS	-	5 years[a]	ELISA 6E10 R182 R165	-	↑ baseline $A\beta_{1-42}$	HR = 2.6
Schupf *et al*. 2010 [33]	61 DSp 164 cnDS	53.7 50.3	-	ELISA 6E10 R182 R165	-	Decrease of $A\beta_{1-40}$ Stable $A\beta_{1-42}$ Decrease $A\beta_{1-42}$ Stable $A\beta_{1-42}/A\beta_{1-40}$ Decrease $A\beta_{1-42}/A\beta_{1-40}$	HR = 0.4 HR = 2.6 HR = 4.9 HR = 3.9 HR = 4.9
Coppus *et al*. 2012 [54]	79 DSp 264 cnDS	53.3 50.6	-	xMAP INNO-BIA	-	↑ baseline $A\beta_{1-40}$ ↑ baseline $A\beta_{1-42}$	HR = 2.05 HR = 2.56

[a]Estimated by author of review. cnDS, cognitively normal Down syndrome; CV, coefficient of variation; DSp, Down syndrome subjects who progress to a dementia diagnosis; HR, hazard ratio.

plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ at baseline. Two studies found an interaction between cognitive reserve and Aβ plasma levels, indicating that subjects with lower cognitive reserve showed a greater decline associated with Aβ levels [10,65].

Longitudinal sampling of Aβ plasma measures

A small number of studies have included repeated sampling of plasma Aβ levels [10,27,29,57]. In the study by Mayeux *et al.* [27], a general increase was found for plasma $A\beta_{1-40}$ over time, and plasma $A\beta_{1-40}$ levels in CN stable subjects showed an increase over time, while incident and baseline AD subjects showed a decrease over time. A second study of the same group reported an increased incidence of dementia in CN subjects who showed a decrease in $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$ during follow-up [57]. The study of Okereke *et al*. [64] found that a decrease in $A\beta_{1-42}/A\beta_{1-40}$ in the repeated plasma measurement was associated with greater cognitive decline. Lastly, studies reported by Hansson *et al.* [29] and Toledo *et al.* [10] found that during follow-up of 324 subjects for 5 years in the former and 613 subjects for 2 to 3 years in the latter study, there was an increase of $A\beta_{1-40}$ and $A\beta_{1-42}$, whereas $A\beta_{1-42}/A\beta_{1-40}$ decreased.

Aβ plasma measures and cerebrovascular disease

An association between plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ levels in APOE ε4 carriers and in subjects known to have lacunar infarcts and white matter hyperintensities has been described in the Rotterdam study [28]. A second study that included subjects with cerebral amyloid angiopathy, MCI and AD also found an association between increased Aβ plasma and the presence of white matter hyperintensities and lacunar infarcts [68]. A third study specifically analyzed the association between microbleeds and plasma Aβ levels in subjects with AD and vascular dementia [69]. In this study, patients with nonlobar hemorrhages, located in the deep gray matter region and associated with hypertensive vasculopathy, showed higher $A\beta_{1-40}$ plasma levels compared to subjects with lobar hemorrhages, which are associated with cerebral amyloid angiopathy. In the ADNI cohort, we found no association between Aβ plasma levels and white matter hyperintensities, but subjects with infarcts on MRI had higher plasma $A\beta_{1-42}$ levels [10]. Finally, a longitudinal study by Lambert *et al.* [59] reported a higher incidence of vascular dementia in subjects with a low $A\beta_{1-42}/A\beta_{1-40}$.

Aβ plasma measures as biomarkers in clinical trials

Repeated sampling and measurement of plasma Aβ levels have been used to monitor the pharmacodynamic response of subjects in clinical trials of γ-secretase inhibitors (GSIs) and modulators (GSMs) as well as for passive immunotherapy. Studies in subjects treated with GSIs showed an initial dose-dependent decrease of total Aβ and $A\beta_{1-40}$ levels that was followed by a dose-independent increase of both analytes [70,71]. A model based on a hypothetical inhibition of α-secretase by increases in C99 associated with GSI treatment has been proposed in order to explain these changes, but this remains to be proven [72]. Both studies by Siemers *et al.* [70,71] did not report changes in CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ levels, although the second sample was taken 4 hours after treatment and a longer timeframe might be needed to assess changes in the CSF levels of these Aβ species. Due to the worse cognitive outcome and secondary effects (severe gastrointestinal toxicity, immunomodulation and skin cancer) in patients treated with GSIs [73], research in this area has shifted towards GSMs that spare Notch signaling. These GSM have also shown a decrease of plasma Aβ [74-76] but the results regarding any Aβ-rebound are contradictory for GSMs [75,76]. On the other hand,

Table 3. Cross-sectional studies in populations including sporadic Alzheimer's disease patients

Study	Subjects	Mean age (years)	Platform and antibodies	CV	Values in AD patients			Other
					$A\beta_{1-40}$	$A\beta_{1-42}$	$A\beta_{1-42}/A\beta_{1-40}$	
Mehta *et al.* 2000 [55]	61 CN 78 AD	67 74	ELISA 6E10 R162 R164	<18%	↑	=	-	
Mayeux *et al.* 2003 [27]	79 AD 365 CN	83.2 75.5	ELISA 6E10 R182 R165	-	=	↑	NA	
Fukumoto *et al.* 2003 [26]	92 CN 96 PD 37 MCI 146 AD	69 66.0 72.6 76	ELISA Takeda	<10%	=	=	=	
Assini *et al.* 2004 [41]	72 CN 88 MCI	73 75	ELISA IBL	-	-	-	-	Increased $A\beta_{1-42}$ in MCI women
Lewczuk *et al.* 2010 [56]	137 MCIp 62 MCI-OD 127 AD 25 OD	67.4 63.3 70.8 66.6	xMAP INNO-BIA	<10%	-	-	-	MCI and AD with AD-like CSF ↓ $A\beta_{1-42}$ & ↓ $A\beta_{1-42/}$ $A\beta_{1-40}$
Lui *et al.* 2010 [14]	724 CN 122 MCI 186 AD	70.0 75.9 78.6	ELISA Mehta xMAP INNO-BIA	-	=	↓	=	
Le Bastard *et al.* 2010 [12]	47 CN 50 non-AD 47 AD	69 74 82	xMAP INNO-BIA	<10%	=	=	=	↓$A\beta_{1-42}/A\beta_{N-42}$
Toledo *et al.* 2011 [10], Figurski *et al.* 2012 [48]	187 CNs 10 CNp 162 MCIs 145 MCIp 162 AD	75.8 78.4 74.7 74.6 75.3	xMAP INNO-BIA	<10%	=	=	=	Interaction between age and diagnosis defined by CSF

AD, Alzheimer's disease; CN, cognitively normal; CNp, cognitively normal progression; CNs, cognitive normal stable; CV, coefficient of variation; MCI, mild cognitive impairment; MCI-OD, mild cognitive impairment, progression to non-AD dementia; MCIp, mild cognitive impairment progressor (to AD); MCIs, mild cognitive impairment stable; NA, not available; OD, other dementia; PD, Parkinson's disease.

passive immunotherapy results from clinical trials suggest that there is a dose-dependent transient increase of plasma Aβ in response to the monoclonal anti-Aβ antibody infusion and this was reported to last several weeks [77]. Thus, more research is clearly needed to elucidate the effects of these disease-modifying therapies on plasma Aβ levels.

Conclusions

Plasma Aβ is well known to originate in different organs and it also is known that Aβ binds to different proteins and cells in the blood, thereby possibly accounting for why plasma Aβ levels do not correlate with Aβ measured in CSF or CNS plaque burden measured by PET amyloid plaque imaging. Levels of plasma Aβ increase with aging and some clinical associations may change depending on the age of the selected sample. The selection of capture antibodies and analytical platforms can have an important impact on the measured Aβ levels; a wide range of mean $A\beta_{1-40}$ (214 [15] to 985 pg/ml [40]) and $A\beta_{1-42}$ (36 [15] to 140 pg/ml [19]) levels in AD patients has been reported in different studies and this also is the case for studies of CN subjects. Moreover, even in studies that use the same analytical platform and capture antibodies, there are important differences in the measured Aβ levels, which could be attributed to pre-analytical and analytical factors [10,42-44,48]. A recent study showed that automating multiple pipetting steps in a commercially available immunoassay that measures $A\beta_{1-42}$ and $A\beta_{1-40}$ provided better precision, thus leading to standardization of reagent dispensing in this test system [48]. Therefore, standardization efforts such as this and

Table 4. Longitudinal studies in populations including sporadic Alzheimer's disease patients

Study	Subjects	Mean age at baseline (years)	Duration of follow-up (years)	Platform and antibodies	CV	Analyte associated with increased risk conversion to AD	Magnitude
Mayeux *et al*. 1999 [30]	105 CNs 64 CNp	73.4 77.4	3.5	ELISA 6E10 R182 R165	-	High baseline $A\beta_{1-42}$	HR = 3.6-4.0
Mayeux *et al*. 2003 [27]	365 CNs 86 CNp	75.5 79.3		ELISA 6E10 R182 R165	-	High baseline $A\beta_{1-42}$	1.9-2.4
van Oijen *et al*. 2006 [61]	1364 CNs 289 CNp 103 CNp-OD		8.5	ELISA 6E10 R226 R209	<15%	High baseline $A\beta_{1-40}$ Low baseline $A\beta_{1-42}/A\beta_{1-40}$	HR = 1.17 HR = 1.82
Graff-Radford *et al*. 2007 [58]	510 CNs 53 CNp	-	5	ELISA BAN-50 BA27 BC05	-	Low baseline $A\beta_{1-42}/A\beta_{1-40}$	RR = 2.47-3.08
Lopez *et al*. 2008 [63]	117 CNs 115 CNp 9 MCIs 33MCIp	78.6 79.9 80.5 79.6	4.5	ELISA	-	None	-
Sundelöf *et al*. 2008 [62]	608CNs 74 CNp	-	11.2	ELISA BNT77 BA27 BC05	-	Low baseline $A\beta_{1-40}$ (only in the cohort older than 77 at baseline)	HR = 4.9
Schupf 2008 [57]	104 MCIp 1021 CNs	80.7 76.3	4.5	ELISA 6E10 R182 R165	-	High baseline $A\beta_{1-42}$ Decrease of $A\beta_{1-42}$ Decrease of $A\beta_{1-42}/A\beta_{1-40}$	HR = 2.3-3.5 HR = 2.6 HR = 3.4
Lambert *et al*. 2009 [59]	985 CNs 233 CNp	73.8 77.9	4	xMAP INNO-BIA	-	Low baseline $A\beta_{1-42}/A\beta_{1-40}$	HR = 2.0
Blasko *et al*. 2010 [78]	122 CNs 33 CNp	-	5	ELISA INNOTEST	<17%	High baseline $A\beta_{1-42}$	OR = 1.7
Hansson *et al*. 2010 [13]				xMAP INNO-BIA	<10%	No differences	
Toledo *et al*. 2011 [10]	162 MCIs 145 MCIp	74.7 74.6	3.0	xMAP INNO-BIA	<10%	None	
Shah *et al*. 2012 [60]	590 CNs 53 MCIp 24 MCIp-VaD	-	15.8	ELISA 2G3 21F12	<20%	Low baseline $A\beta_{1-40}$ Low baseline $A\beta_{1-42}$	HR = 2.1 HR = 1.6
Hansson *et al*. 2012 [29]	677 CNs 37 MCIp 11 MCIp-VaD 5 MCIp-OD	73.1 77.3 78.9 78.8	5	xMAP INNO-BIA	<10%	High baseline $A\beta_{1-40}$	OR = 2.2

AD, Alzheimer's disease; CNs, cognitively normal stable; CNp, cognitively normal progression; CNp-OD, cognitively normal progression to non-AD dementia; CSF, cerebrospinal fluid; HR, hazard ratio; MCIp-OD, mild cognitive impairment, progression to non-AD dementia; MCIp, mild cognitive impairment progressor (to AD); MCIp-VaD, mild cognitive impairment, progression to vascular dementia; MCIs, mild cognitive impairment stable; OD, other dementia; OR, odds ratio; RR, relative risk.

similar to the ones undertaken in the field of CSF Aβ measurements are needed [47]. Thus, this variability precludes the possibility of establishing diagnostic or prognostic cut-offs across different studies and populations until these assays are better standardized.

Using the profile of CSF tau and Aβ levels to define groups that have an underlying AD pathology reveals associations between subjects with and without AD-like CSF irrespective of a clinical diagnosis of CN, MCI or AD. Clinical diagnosis in the absence of a neuropathological validation or a CSF Aβ levels/PET plaque load validation may underestimate and confound the diagnostic/prognostic value of plasma Aβ measurements [2]. Cerebrovascular disease, which is a frequent finding in aged populations, is another important factor that can affect plasma Aβ levels and the prevalence of vascular risk factor and vascular disease varies considerably in the different samples according to the design of the study. While not useful as a diagnostic biomarker as shown by the cross-sectional studies, repeated Aβ plasma measurements in the same individual over time could become useful as a prognostic biomarker. Longitudinal studies favor the 'peripheral sink' hypothesis with a decrease of plasma levels starting in the dementia stage in contrast to an increase of plasma Aβ during the pre-symptomatic stage so that disease stage-specific changes later in the course of AD may explain previously described conflicting results. Although the reported differences or changes in Aβ plasma levels might not be large enough to predict the longitudinal outcome, it is potentially possible that this biomarker can serve as a prognostic factor or as an endpoint during follow-up of AD patients. However, prospective studies of cohorts with subsequent neuropathology confirmation of their diagnosis or in concert with data on CSF tau and Aβ levels as well as other biomarker data are needed to establish how to best interpret data on plasma Aβ levels in CN, MCI and AD subjects with and without other comorbid conditions such as cerebrovascular disease.

This article is part of a series on *Peripheral Biomarkers*, edited by Douglas Galasko. Other articles in this series can be found at http://alzres.com/series/biomarkers

Abbreviations

Aβ, amyloid beta; AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; APP, Aβ precursor protein; AV-45, florbetapir-F18; CN, cognitively normal; cnDS, cognitively normal Down syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; CV, coefficient of variation; dDS, demented Down syndrome; DS, Down syndrome; ELISA, enzyme-linked immunosorbent assay; FAD, familial Alzheimer's disease; GSI, γ-secretase inhibitor; GSM, γ-secretase modulator; MCI, mild cognitive impairment; PET, positron emission tomography; PiB, Pittsburgh Compound-B-C11;

Competing interests

The authors declare that they have no competing interests.

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