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Plasma Aβ42 and Aβ40 as markers of cognitive change in follow-up: a prospective, longitudinal, population-based cohort study

T T Seppälä, S-K Herukka, T Hänninen, S Tervo, M Hallikainen, H Soininen, T Pirttilä

ABSTRACT
Background Single measurements of plasma Aβ are not useful in the diagnostics of Alzheimer's disease (AD). However, changes in plasma Aβ levels during repeated testing may be helpful in the prediction and evaluation of progression of the incipient AD or mild cognitive impairment.

Objective To examine the relation of baseline and serial plasma Aβ levels to cognitive change in follow-up.

Methods 269 subjects (52 cognitively impaired and 217 controls) from a population-based cohort were clinically followed up from 3 to 6 years. Serial plasma samples were available from 70 subjects who were followed up for 3 years and 43 subjects followed for 6 years. The plasma Aβ levels were measured using EUSIA.

Results Subjects who declined cognitively during the follow-up had lower levels of plasma Aβ42 at the baseline. Plasma Aβ42 and the Aβ42/Aβ40 ratio decreased (2.4 pg/ml for Aβ42 in 6 years) in those who declined in follow-up, whereas Aβ42 and the Aβ42/Aβ40 ratio increased in the subjects who remained cognitively stable or improved in follow-up. Subjects using acetylsalicylic acid, dipridamole, antidiabetic or anticoagulant drugs as well as subjects with coronary heart disease had higher levels of Aβ40.

Conclusions Low or decreasing plasma Aβ42 during the follow-up is associated with cognitive decline. Serial measurement of plasma Aβ42 may be useful in the detection of the subjects who are at risk for cognitive decline.

INTRODUCTION
Alzheimer’s disease (AD) is the most common cause of dementia. At present, its diagnosis is based on clinical criteria and the exclusion of other causes. However, objective biomarkers for the early diagnosis and monitoring of the disease process are clearly needed because symptomatic treatments are available, and disease-modifying drugs are already in phase III trials. The presence of amyloid β deposition in senile plaques is one pathological hallmark of Alzheimer’s disease (AD) together with neurofibrillary tangles.1 The amyloid β is a peptide secreted by neurons1 and platelets,2 derived from amyloid precursor protein APP via the activity of proteases β and γ secretes.3 Most of the Aβ deposited in the brain is composed of 42 amino acids (Aβ42) form.4 Aβ42 has also been shown to be the first amyloid form to accumulate with Aβ40 being deposited later in the process of AD pathogenesis.5

The level of Aβ42 in cerebrospinal fluid (CSF) is reduced in patients with mild cognitive impairment (MCI) and AD,6,7 and a combination test of CSF Aβ42 and τ or phospho-tau has been claimed to be helpful in the early diagnosis of AD.8

Aβ is present in plasma, but it is still unknown whether it originates from peripheral sources or from the brain. In Tg2576 transgenic mouse, plasma Aβ levels decline in parallel with their increasing accumulation in the brain.9 Since Aβ can be transported bidirectionally across the blood–brain barrier, it has been hypothesised that there may be an equilibrium between CSF and plasma pools of Aβ.10,11 Seeing that it is well established that CSF Aβ42 levels decrease in conjunction with the cognitive decline, it has been postulated that plasma Aβ42 may decrease similarly.12 If so, plasma Aβ would offer a straightforward, non-invasive and economical biomarker for AD. However, patients with known mutations in chromosome 21 causing early-onset familial AD as well as patients with trisomy 21 have increased plasma Aβ42 levels which are detectable before the onset of the symptoms of dementia.13,14 Also, the first-degree relatives of late-onset AD patients exhibit elevated Aβ levels measured in plasma.15

Previous studies have suggested that the levels of plasma Aβ40 are increased before the onset of sporadic AD.16,17 However, one recent study concluded that low plasma Aβ40 level predicted AD in older men.18 Other studies have found elevated Aβ42 levels in patients who later develop dementia,19 particularly in MCI amnestic type (aMCI).20 Finally, several studies have not been able to detect any significant difference of Aβ levels between AD converters and cognitively stable controls.21–22

It seems that a single measurement of plasma Aβ is not useful, whereas the change in plasma Aβ levels observed in repeated testing may be of help in the prediction and evaluation of progression of incipient AD or MCI.23 However, only a limited number of longitudinal studies have been performed.24–28 Our aim was to examine whether the change in plasma Aβ levels during follow-up would be more predictive of cognitive decline than straightforward baseline plasma Aβ levels in a population-based cohort of MCI and cognitively intact controls.

SUBJECTS AND METHODS
Subjects
Study subjects were participants in the population-based study (n=806, aged 60–76 years) examining the risk factors and predictors of dementia in older people27,28 (table 1). At baseline (years 1997–1998), 52 subjects were cognitively impaired (Clinical Dementia rating (CDR) 0.5 n=51 and CDR 1 n=1). Group 1 of this study included all of the cognitively impaired subjects from the original cohort who
provided a plasma sample (n=52). For each of them, we randomly selected 4–5 cognitively unimpaired (n=217) age- and sex-matched controls from the same cohort. These subjects were clinically re-evaluated after 3 years (n=197) and 6 years (n=60).

The longitudinal marker group (group 2) included 70 subjects of the original cohort of 269 subjects who provided a 3-year follow-up plasma sample and 43 of them a 6-year follow-up sample. Group 2 included 11 cognitively impaired (at baseline) non-demented subjects (CDR 0.5) who provided at least one follow-up plasma sample and 59 cognitively intact (at baseline) age- and sex-matched controls with at least one follow-up plasma sample (figure 1). Drop-outs occurred mainly due to a refusal of the participants to continue the study. Written informed consent was obtained from all the subjects, and the study was approved by the local Ethical Committee.

**Clinical evaluation**

The evaluation included a structured detailed interview including demographic information, medical history, medication, smoking habits and alcohol consumption, and a subjective assessment of memory disturbances and depression. The evaluation also included clinical examination as well as an assessment of cognitive impairment by applying the CDR and using a battery of neuropsychological tests: Memory: Visual Reproduction Test from Wechsler Memory Scale,29 Word List Recall from the Constructional Praxis Test from Wechsler Memory Scale,29 Word List Recall of the Constructional Praxis from CERAD;30 Language: vocabulary subtest from the Wechsler Adult Intelligence Scale-Revised,33 Abbreviated (15 items) Boston Naming Test;34 Attention and executive function: Trail Making Test35 parts A and B, Verbal Fluency Test;36,37 Visuospatial skills: Block Design from the WAIS-R,33 Constructional Praxis from CERAD,30 Global functioning: Mini-Mental State Examination38 (MMSE) Clock Drawing Test.30

Cognitive decline was defined by the CDR change from 0 to 0.5 or 0.5 to 1.

**Measurement of Aβ40 and Aβ42**

The 269 baseline samples (group 1) were measured in year 2002–2003. After completing the 6-year follow-up, we reanalysed the baseline samples of 70 subjects (group 2) together with their follow-up samples in year 2006–2007 (group 2).

A venous blood sample was obtained into heparin tubes, and plasma was separated using standard methods. The samples were aliquotted and stored in polypropylene tubes at −70°C until analyses. Aβ40 was measured by the ELISA method modified from a well-established method.16 The capture antibody was 6E10 (Sigma, St Louis, Missouri), and the detection antibody was a biotin-labelled G2-10 antibody (The Genetics Company, Schieren, Switzerland). The synthetic Aβ1–40 peptide (Bachem, Bubendorf, Switzerland) was used as the standard. Before the analyses, 0.05% Tween 20–0.5% BSA was added to the samples. Aβ42 was measured by a high-sensitivity method of a commercially available ELISA (Innogenetics, Gent, Belgium) which we modified to be suitable for the measurements of concentrations higher than 7 pg/ml. Before the analyses, 0.5 M guanidine chloride was added to the standards and samples. The detergents were used to avoid coagulation of samples and to release Aβ peptides from plasma proteins.

In a longitudinal analysis, baseline and follow-up samples from one individual were placed on the same plate to prevent interassay variation. Thus, we measured baseline samples from 70 subjects twice (4 years apart). The absolute concentrations differed between these two measurements; median level for Aβ40 174.5 pg/ml (year 2003) and 198 pg/ml (74) (year 2007), and Aβ42 17 pg/ml (year 2005) and 49 pg/ml (110) (year 2007). However, there was a moderately good correlation between these measurements (Aβ40 r=0.67, p<0.001 and Aβ42 r=0.824, p<0.001). The correlation figure is presented in the supplemental data (available at http://www.jnnp.com).

The interassay variation for the Aβ40 assay was 23.8% and for the Aβ42 assay 19.1%. The inter-CVs were measured using reference samples of medium concentration (~250 pg/ml for Aβ40 and ~400 pg/ml for Aβ42). The intra-assay variations for Aβ40 were 0.71% for high (~1200 pg/ml), 0.95% for medium and 5.9% for low concentrations (~150 pg/ml). The intra-assay

### Table 1 Baseline demographic information of the subjects

|                      | Population-based cohort | Group 1 (cognitive follow-up) | Group 2 (plasma follow-up) |
|----------------------|--------------------------|-------------------------------|-----------------------------|
| n                    | 806                      | 269                           | 70                          |
| Age                  | 68 (60–76)               | 70 (60–77)                    | 71 (61–77)                  |
| Men/women            | 321/485 47%              | 121/148 45%                   | 25/45 36%                   |
| APOE ε4 −/+/−/+       | 414/207* 67%/33%         | 168/99† 63%/37%              | 37/33 53%/47%              |
| Mini-Mental State Examination | 26 (7–30)     | 27 (13–30)                    | 26 (17–30)                  |
| CDR                  | 731                      | 217                           | 59                          |
| CDR = 0.5            | 70                       | 51                            | 11                          |
| CDR = 1†             | 3                        | 1                             | 0                           |

Data are given as median values (range) or as number of subjects with the percentage of all subjects in the group.

*APOE data missing from 185 subjects.
†APOE data missing from one subject.
‡One subject had CDR 2. Data missing from one subject.

CDR, Clinical Dementia rating.

**Figure 1** Formation of the study population.

**Table 1** Baseline demographic information of the subjects.
CVs (median) for Aβ42 were 1.6% (~1000 pg/ml), 2.5% and 9.8% (~15 pg/ml), respectively.

APOE genotyping

The APOE allele genotyping was done by a PCR-based method. The subjects were subdivided into the APOE ε4 negative and APOE ε4 positive subjects.

Statistics

The statistical analyses were conducted using SPSS for Windows release 14.0.1 (SPSS, Chicago, Illinois). Due to the non-normal distribution of data, Kruskal–Wallis, Mann–Whitney U and Spearman correlation tests were used. The categorical data were analysed by the χ² test. The ORs for cognitive decline of patients in different groups were calculated by logistic regression analysis. We fitted a linear regression slope by Microsoft Excel to analyse the alteration trend of Aβ levels.

RESULTS

Table 1 presents the demographic information about the subjects. The baseline Aβ40 and Aβ42 levels of 269 individuals were generally low, although some subjects exhibited extremely high Aβ42 levels. The limit for the 90th percentile was 101 pg/ml, but the highest measured level was 1541 pg/ml. The Aβ40 levels showed a weak correlation with age (r = 0.186, p = 0.002), but this was not the case with the Aβ42 levels. There were no differences in Aβ40 and Aβ42 levels between the sexes or between the APOE ε4 carriers and non-carriers. Aβ42 levels did not correlate with Aβ40 concentrations.

Baseline Aβ levels and cognitive decline during the follow-up

No significant differences were found in plasma Aβ40, Aβ42 or the Aβ42/Aβ40 ratio between cognitively impaired (n=52) and cognitively intact subjects (n=217) at baseline.

However, 197 of these subjects were clinically assessed after 3 years, and 60 were clinically assessed after 6 years. The baseline Aβ42 levels were significantly lower in the subjects who showed cognitive decline after 3 years of follow-up (cognitively stable, n=147: 19 pg/ml (0–1541), cognitive decline, n=50: 12 pg/ml (0–276), p=0.001). Baseline Aβ42 levels were also lower in subjects who had declined cognitively after 6 years (10 pg/ml, n=50) compared with those who remained cognitively stable (18 pg/ml, n=24), p=0.013.

Subjects who had baseline Aβ42 levels in the lowest quartile displayed an OR of 3.12 (95% CI 1.25 to 7.79, p=0.015) for cognitive decline after 3 years and 4.77 (95% CI 1.14 to 19.98, p=0.053) after 6 years in comparison with subjects who had Aβ42 levels in the highest quartile. Similarly, subjects who had an Aβ42/Aβ40 ratio in the lowest quartile had an OR of 3.26 (1.31 to 8.11, p=0.011) for cognitive decline after 3 years and 8.40 (1.83 to 33.56, p=0.006) after 6 years of follow-up when compared with the subjects in the highest quartile.

Relationship between changing plasma Aβ levels and cognitive decline

The follow-up plasma samples were available from 70 subjects after 3 years and 45 subjects after 6 years of follow-up. The median levels of Aβ42 did not change or decreased in subjects with cognitive decline (n=27 after 3 years and n=14 after 6 years), whereas they increased in those who remained cognitively stable (table 2). No statistically significant changes were found in Aβ40 levels. The Aβ42/Aβ40 ratio decreased significantly in the subjects who experienced a cognitive decline.

A trend analysis was undertaken by calculating a slope for each subject, and this was used to assess the change of Aβ42 between cognitively stable and cognitively declining subjects. During the follow-up of 3–6 years, the cognition of 28 out of the total 70 subjects had declined, and there was a decreasing trend in the level of Aβ42 in 24 subjects during the follow-up. The Aβ42 level remained the same in the declining subjects and increased in the cognitively stable subjects (0.0 (4.9) pg/ml/year and 2.1 (21) pg/ml/year; p=0.009 for slope difference). The corresponding changes of Aβ42/Aβ40 ratio were also significant (0.0 (0.029) per year and 0.0056 (0.055) per year; p=0.02 for slope difference).

Plasma Aβ and general health

Table 3 shows the relationship between medication as well as certain diseases on the plasma Aβ levels. The Aβ40 levels were not associated with the use of lipid-lowering drugs or non-steroidal anti-inflammatory drugs (NSAIDs) at baseline. Hormone-replacement therapy was not related to Aβ values in women. The Aβ40 levels were higher in those subjects using acetylsalicylic acid (ASA) (n=62, p=0.004) or dipyridamole (n=12, p=0.017). The Aβ40 values were lowest in subjects using neither of the drugs, intermediate in subjects using either ASA or dipyridamole and highest in the subjects taking both drugs. The Aβ40 levels were also higher in subjects using insulin alone (n=5, p=0.009) or insulin in combination with oral antidiabetic drugs (n=13, p=0.005). The Aβ42 levels were not associated with the use of any of the drugs. Coronary heart disease was associated with a high plasma Aβ40 level (p=0.035). There was

Table 2 Cognition and changes of Aβ between baseline and follow-ups in subjects

| Baseline          | Cognitively healthy | Cognitively impaired |
|-------------------|---------------------|----------------------|
| N                 | 59                  | 11                   |
| Aβ40              | 195 (88)            | 201 (60)             |
| Aβ42              | 50 (121)            | 46 (92)              |
| Aβ42/Aβ40         | 0.236 (0.464)       | 0.291 (0.487)        |

| Follow-up         | 3 years | 6 years | 3 years | 6 years |
|-------------------|---------|---------|---------|---------|
| N                 | 43†     | 29‡     | 27      | 14      |
| Change of Aβ40    | 18 (55) | 33 (45) | 21 (24) | 33 (75) |
| Change of Aβ42    | 3.7 (29) | 12 (54) | 0.0 (14)* | –2.4 (50)* |
| Change of Aβ42/Aβ40 | 0.0093 (0.169) | 0.0166 (0.451) | –0.0027 (0.084)* | –0.0486 (0.251)* |

Data are given as medians (IQR). The values of p reflect the significance against the cognitively stable subgroup.

*p < 0.05 against ‘stable or improved.’

†Aβ data of one subject is from a plasma sample of 4 years of follow-up.

‡Cognition data of two subjects is from the previous year.
with cognitive decline.\textsuperscript{17} Other studies have reported different
results. The VITA study found no association between baseline
plasma A\textsubscript{β} levels and A\textsubscript{β}42/A\textsubscript{β}40 ratio and cognitive decline.\textsuperscript{19} 42
Recent study detected an association between a low A\textsubscript{β}42/A\textsubscript{β}40 ratio and cognitive decline.\textsuperscript{12} Respectively, a prospective three-city
study of 257 dementia patients found an association of high
A\textsubscript{β}42/A\textsubscript{β}40 ratio with a lower risk of dementia in follow-up.\textsuperscript{43}
Another population-based case-cohort study claimed that indi-
viduals with a combination of low A\textsubscript{β}42 and high A\textsubscript{β}40 measured
from plasma at baseline had more than a 10-fold risk of dementia
but found no association between the A\textsubscript{β}42 or A\textsubscript{β}40 levels alone
with cognitive decline.\textsuperscript{17} Other studies have reported different
results. The VITA study found no association between baseline
A\textsubscript{β} levels and cognitive decline during the follow-up.\textsuperscript{42} Other
studies have found elevated concentrations of A\textsubscript{β}42 at the base-
line in subjects who developed AD during the follow-up,\textsuperscript{19} 42
although plasma A\textsubscript{β} levels were not associated with AD in the
fully adjusted multivariate model.\textsuperscript{42}

Differences in study cohorts, for example timing with respect
to cognitive decline, assessment of cognitive functioning
(different tests) and presence of confounding factors such as
medication and other diseases, are all factors that can influence
the results. The outcome in some studies has been conversion
to dementia,\textsuperscript{17} 19 whereas the outcome in our study as well as in
some other studies\textsuperscript{12} was cognitive decline. The difference in the
selected outcome and the timing of the sample collection may
partially explain differences in the results.

Single measurement of plasma A\textsubscript{β} may not be a suitable
marker for AD due to many confounding factors. The timing of
the A\textsubscript{β} measurement in terms of the natural history of AD may
be critical. Experimental studies on transgenic animals suggest
that plasma A\textsubscript{β} levels decrease at the time when accumulation
of A\textsubscript{β} begins in the brains.\textsuperscript{9} It is possible that the increased
plasma A\textsubscript{β} concentration is related to the development of AD as
suggested by the findings of elevated plasma A\textsubscript{β} levels in AD
gene mutation carriers\textsuperscript{44} and in the first-degree relatives of the
patients with late-onset AD.\textsuperscript{15} However, since amyloid
pathology in the brain begins years before the appearance of the
first symptoms, the possible increase in plasma A\textsubscript{β} may not be
detected in the symptomatic individuals. This hypothesis
can only be addressed in longitudinal studies. In line with our
results, previous studies have suggested that decreasing A\textsubscript{β} levels
are associated with cognitive decline,\textsuperscript{19} 24 and A\textsubscript{β}42 levels were
lower in patients diagnosed having AD than in those with MCI.\textsuperscript{44} Many studies have shown that plasma A\textsubscript{β} levels increase
with age, as was found in the cognitively intact subjects in our
study.\textsuperscript{19} 25 42 In one study, the age-related increase was smallest
in those subjects who converted to AD from MCI.\textsuperscript{25} It is
possible that age-related changes of plasma levels of A\textsubscript{β}40 and
A\textsubscript{β}42 differ in subjects with AD. In this respect, the A\textsubscript{β}42/A\textsubscript{β}40
ratio may be a better predictor for AD than the single markers.

Differences in study cohorts make the comparison between
different studies difficult. There are many confounding factors
that may influence plasma A\textsubscript{β} levels. Renal dysfunction may
increase plasma, since plasma A\textsubscript{β} is excreted through the
kidneys.\textsuperscript{45} Many studies have suggested an association between
vascular disease and plasma A\textsubscript{β} levels.\textsuperscript{46–48} The levels of plasma
homocysteine, a possible marker for vascular disease, correlate
positively with plasma A\textsubscript{β}40 and A\textsubscript{β}42 levels.\textsuperscript{49} Previous studies
have also suggested that certain drugs may influence plasma
A\textsubscript{β}.\textsuperscript{50} We found elevated levels of A\textsubscript{β}40 in the subjects who were
using ASA and dipyridamole, that is drugs that directly influence
platelet function and activation, and subjects who used anti-
coagulation and antiobiotic drugs, whereas there was no asso-
ciation between the use of NSAIDs or lipid-lowering agents and
plasma A\textsubscript{β} levels. The association between ASA and plasma
A\textsubscript{β}40 was seen also in subjects without cardiovascular diseases.
In line with previous studies,\textsuperscript{50} 51 no relationship was found
between A\textsubscript{β} levels and lipid-lowering agents in previous studies.

Differences in methodology and experimental conditions may
also influence results. Erythrocytes and plasma proteins, for
example albumin and lipoproteins, bind A\textsubscript{β} and denaturating
conditions liberate A\textsubscript{β} into the free pool of plasma.\textsuperscript{52} Also, the
different antibodies used in the immunological assays may
detect different fractions of A\textsubscript{β}. Previous studies suggested that
the absolute levels of A\textsubscript{β} vary across different ELISA batches.\textsuperscript{53}
We also noticed a difference between absolute levels in 70
tables that were measured twice 4 years apart. Because of these
methodological difficulties, the diagnostic value of a single
measurement is limited.

The significance of the standardisation of the conditions in
storing and handling the samples is reported in a study by
Vanderstichele et al.\textsuperscript{22} To better utilise these analyses, the assays
used should be commercially available, well standardised and
thoroughly validated.

We conclude that plasma A\textsubscript{β} is not a diagnostic marker for
AD, but the decreasing levels of A\textsubscript{β}42 in serial measurements
may be associated with cognitive decline and indicate the
development of AD.

**Table 3** Relation of A\textsubscript{β}40 level to medication at baseline

| Group 1 | A\textsubscript{β}40 | pg/ml Users | pg/ml Non-users |
|---------|----------------|----------------|----------------|
| n       |                |                |                |
| Sex, female | 148 | –           | –              |
| Smoking | 21           | –              | –              |
| Coronary heart disease | 61 | ↑ | p=0.035 188 (105–360) 176 (0–780) |
| Diabetes | 22           | –              | –              |
| Anticoagulants | 16 | ↑ | p=0.038 198 (144–360) 176 (0–780) |
| Non-steroidal anti-inflammatory drugs | 22 | – | – |
| Acetylsalicylic acid | 62 | ↑ | p=0.004 194 (0–278) 175 (0–780) |
| Dipyridamole | 12 | ↑ | p=0.016 208 (156–278) 176 (0–780) |
| Anti-diabetics* | 13 | ↑ | p=0.003 219 (161–426) 179 (0–780) |
| Lipid-lowering agents | 24 | – | – |

*Insulin and oral antidiabetics.

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