

## Plasma Amyloid $\beta$ (A $\beta$ <sub>42</sub>) Correlates with CSF A $\beta$ <sub>42</sub> in Alzheimer's Disease

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**Abstract.** The 42 amino acid form of amyloid  $\beta$  (A $\beta$ <sub>42</sub>) plays a key role in the pathogenesis of Alzheimer's disease (AD) and is a core biomarker for the diagnosis of AD. Numerous studies have shown that cerebrospinal fluid (CSF) A $\beta$ <sub>42</sub> concentrations

are decreased in AD, when measured by enzyme-linked immunosorbent assay (ELISA) and other conventional immunoassays. While most studies report no change in plasma A $\beta$ <sub>42</sub>, independent studies using the immunomagnetic reduction (IMR) technique report an increase in plasma A $\beta$ <sub>42</sub> levels in AD. To confirm the opposite changes of A $\beta$ <sub>42</sub> levels in CSF and plasma for AD, we assayed the levels of A $\beta$ <sub>42</sub> in plasma of subjects with known CSF A $\beta$ <sub>42</sub> levels. In total 43 controls and 63 AD patients were selected at two sites: the VU University Medical Center (n = 55) and Sahlgrenska University Hospital (n = 51). IMR and ELISA were applied to assay A $\beta$ <sub>42</sub> in plasma and CSF, respectively. We found a moderately negative correlation between plasma and CSF A $\beta$ <sub>42</sub> levels in AD patients (r = -0.352), and a weakly positive correlation in controls (r = 0.186). These findings further corroborate that there are opposite changes of A $\beta$ <sub>42</sub> levels in CSF and plasma in AD. The possible causes for the negative correlation are discussed by taken assay technologies, A $\beta$ <sub>42</sub> transport from brain to peripheral blood, and sample matrix into account.

Keywords: beta amyloid, cerebrospinal fluid, plasma, immunomagnetic reduction

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## INTRODUCTION

There is a strong demand for fluid-based biomarkers for Alzheimer's disease (AD) in both the research and clinical context, with applications in clinical diagnosis, developing AD-related drugs, and as screening tools in clinical trials, for example in the pre-screen of patients for amyloid positron emission tomography (PET) [1-8]. Quantifications of cerebrospinal fluid (CSF) biomarkers such as A $\beta$ <sub>42</sub>, total tau (t-Tau) and phosphorylated tau (p-Tau) proteins have been incorporated into standard diagnostic guidelines for AD [1,2]. It has been demonstrated that the change in CSF A $\beta$ <sub>42</sub> level happens 10-20 years earlier than the onset of clinical symptoms [3,4]. The CSF A $\beta$ <sub>42</sub> level was found to be significantly reduced in individuals with AD [5-9]. For inclusion of A $\beta$ <sub>42</sub> analysis as the first step in a multiple process to screen preclinical AD, it is important to be able to measure it with a low cost and non-invasive method, such as blood analysis. However, the AD-related biomarkers in blood are very low abundant and thus ultra-sensitive assay technologies are needed to measure AD-related biomarkers in blood samples. This demand motives numerous groups to develop ultra-sensitive assays. Several technologies for peripheral blood analysis have been developed, such as single-molecule array (Simoa), single-molecule counting (SMC), multi-analyte profiling (xMAP) and mass spectrometry (MS)-based quantification [10-15]. So far, the results have been inconsistent showing increased, unchanged or decreased plasma A $\beta$ <sub>42</sub> concentrations in AD and no overall significant change upon meta-analysis [16]. The low levels of A $\beta$ <sub>42</sub> in blood together with its short half life and matrix effects pose strong requirements on the methodologies [17].

An ultra-sensitive immunoassay with high sensitivity and low interference called immunomagnetic reduction (IMR) assay was developed to quantify blood A $\beta$ <sub>42</sub> level [18,19]. According to the results in a Taiwanese cohort, blood A $\beta$ <sub>42</sub> level

measured using IMR is approximately 15 pg/ml in healthy elderly individuals [20]. Interestingly, blood A $\beta$ <sub>42</sub> levels are increased in early AD (specifically mild cognitive impairment (MCI) due to AD and mild AD in the two studies) [20,21]. Importantly, higher blood A $\beta$ <sub>42</sub> level in AD patients than healthy control was also observed in study based on a US patient cohort [22]. The good consistency between the studies in Taiwan and US shows the high reliability and promising utilities of blood-based biomarkers for both research and clinical uses of AD using IMR assay.

According to the published reports by independent groups, significant changes in A $\beta$ <sub>42</sub> level in both CSF and in plasma in AD were found, but with an opposite change in A $\beta$ <sub>42</sub> between CSF (reduced levels) and plasma (higher levels), which implies that there is an inverse correlation for A $\beta$ <sub>42</sub> between CSF and plasma. However, the cohorts in the CSF studies were different from the above studies, precluding the possibility to directly correlate A $\beta$ <sub>42</sub> levels between CSF and plasma in the same cohort. Therefore, in the present study, the levels of plasma A $\beta$ <sub>42</sub> (measured with IMR) were directly compared and correlated with those in CSF (measured with ELISA) in the same cohort, that included 106 samples from 63 AD patients and 43 controls from two independent sites. In addition to examining the correlation in A $\beta$ <sub>42</sub> level between CSF and plasma, possible factors contributing to the correlation are discussed.

## **MATERIALS AND METHODS**

### *Study populations*

Two sites enrolled subjects and analyzed CSF A $\beta$ <sub>42</sub>. The first site was the Clinical Neurochemistry Laboratory, Sahlgrenska University, Mölndal, Sweden, and the samples consisted of de-identified CSF samples from clinical diagnostic routine,

following procedures approved by the Ethical Committee at University of Gothenburg. The AD group included patients with cognitive deterioration who had pathological CSF AD core biomarker levels using optimized cut-off levels for AD, specifically  $A\beta_{1-42} < 530$  pg/ml,  $t\text{-tau} > 350$  pg/ml, and  $p\text{-tau} > 60$  pg/ml [23]. The control group included patients with minor psychiatric or neurological complaints, but with normal basic CSF tests (cell count, CSF/serum albumin ratio, IgG and IgM index), thereby excluding disorders affecting the blood-brain barrier function, including inflammatory CNS disorders [10], together with normal levels of the core AD biomarkers.

The second site was the Alzheimer Center at VU University Medical Center. We selected 53 patients ( $n = 34$  AD patients and  $n = 19$  controls) from the Amsterdam Dementia Cohort [24]. All patients underwent standard dementia screening at baseline, including physical and neurological examination, electroencephalogram (EEG), magnetic resonance imaging (MRI) and laboratory tests. Cognitive screening included at least a Mini Mental State Examination (MMSE). Diagnoses were made by consensus in a multidisciplinary team without knowledge of CSF results. The diagnosis of SCD was given when the results of all clinical examinations and test results were normal, *i.e.*, when the criteria for MCI or AD were not fulfilled, and there was no psychiatric diagnosis. The SCD patients served as a control in this study. All probable AD patients met the core clinical NIA-AA criteria [1]. All subjects gave written informed consent for the use of clinical data for research purposes and the use of clinical data was approved by the local ethical review board.

#### *CSF biochemical analysis*

CSF sampling and analyses followed similar protocols for both sites. In short, CSF was obtained by lumbar puncture, using a 25-gauge needle, and collected in 10 ml polypropylene tubes (Sarstedt, Nümbrecht, Germany). Within two hours, CSF

samples were centrifuged at 1800g for 10 minutes at 4° C. CSF supernatant was transferred to new polypropylene tubes and stored at -20° C until further analysis (within two months). CSF A $\beta$ <sub>42</sub> was measured with a commercially available ELISA (Innotest  $\beta$ -amyloid(1-42); Fujirebio, Ghent, Belgium) on a routine basis as described before [25,26].

#### *Sampling plasma and assaying A $\beta$ <sub>42</sub> in plasma*

Plasma samples were collected by EDTA-blood collecting tube followed by centrifugation with a speed ranges from 1500-2500g for 15 minutes at room temperature. The upper layer (plasma) was then transferred and aliquoted to 1.5 ml microcentrifuge tube and stored at -70 °C or lower until further analysis. Collected plasma samples were then delivered to MagQu Co., Ltd. by dry-ice package for assaying plasma A $\beta$ <sub>42</sub> blindly.

Plasma A $\beta$ <sub>42</sub> concentration was measured by the IMR assay [18,27]. Amyloid  $\beta$  1-42 IMR Reagent (Cat. # MF-AB2-0060; MagQu Co., Ltd., Taiwan) is made of magnetic nanoparticles (Cat. # MF-DEX-0060; MagQu Co., Ltd., Taiwan) and specific antibody (Cat. # ab34376; Abcam, UK) against C-terminal of A $\beta$ <sub>42</sub>. A fixed volume of IMR reagent and plasma sample (60  $\mu$ l: 60  $\mu$ l) were mixed in sample testing tube and assayed with magnetic immunoassay analyzer (Cat. # XacPro-S; MagQu Co., Ltd., Taiwan) at room temperature. The analyzer detects the reduction percentage in the alternating current (ac) magnetic susceptibility  $\chi_{ac}$  of IMR reagent due to the interaction of antibody-coated magnetic nanoparticles and A $\beta$ <sub>42</sub>. The reduction percentage of  $\chi_{ac}$  signal is referred to as the IMR signal. The IMR signal was converted to the concentration of A $\beta$ <sub>42</sub> according to the relationship between IMR signal and A $\beta$ <sub>42</sub> concentration [21,27]. **It is not necessary to dilute EDTA plasma sample for assaying A $\beta$ <sub>42</sub> by IMR, because the plasma A $\beta$ <sub>42</sub> levels of both control and**

AD group are within the assaying range of IMR A $\beta$ <sub>42</sub> assay (0.77-30,000 pg/ml).

#### *Interference test of IMR plasma A $\beta$ <sub>42</sub> assay by A $\beta$ <sub>40</sub>*

Sample contained 100 pg/ml of A $\beta$ <sub>42</sub> (Cat. # A9810; Sigma-Aldrich; USA) was reconstituted and prepared according to user's manual. 100 pg/ml of A $\beta$ <sub>40</sub> (Cat. # A1075; Sigma-Aldrich; USA) was used as interference material and then spiked into sample contained 100 pg/ml A $\beta$ <sub>42</sub>. The A $\beta$ <sub>42</sub> levels were then determined by IMR A $\beta$ <sub>42</sub> assay.

#### *Statistical analysis*

Continuous variables are presented as (mean  $\pm$  standard deviation). Continuous variables were compared using T-test. Spearman correlation done with GraphPad Prism,  $r$ , is performed to explore the correlation between plasma A $\beta$ <sub>42</sub> and CSF A $\beta$ <sub>42</sub> levels.

## **RESULTS**

The demographic information of subjects enrolled at Sahlgrenska University (GOT) and Amsterdam (AMST) is given in Table 1. The mean values and standard deviations of CSF A $\beta$ <sub>42</sub> level detected with conventional ELISA for each site are also shown in Table 1. The average levels of CSF A $\beta$ <sub>42</sub> in AD groups at the two sites were 402.2  $\pm$  105.3 pg/ml (GOT) and 465.2  $\pm$  106.9 pg/ml (AMST), respectively. The CSF A $\beta$ <sub>42</sub> levels for control groups of the two sites were 901.3  $\pm$  177.2 pg/ml (GOT) and 979.7  $\pm$  190.6 pg/ml (AMST), respectively. Combining subjects of the two sites, the CSF A $\beta$ <sub>42</sub> level is 432.2  $\pm$  109.9 pg/ml for AD and 946.9  $\pm$  187.1 pg/ml for CONT, as given in Table 2. The combined AD group showed a significantly lower level of CSF A $\beta$ <sub>42</sub> than the control group ( $p < 0.001$ ).

The specificity of plasma A $\beta$ <sub>42</sub> assay by IMR was clarified by spiking its similarity, A $\beta$ <sub>40</sub>, in sample contained A $\beta$ <sub>42</sub> as interference material. The measured A $\beta$ <sub>42</sub> on samples contained A $\beta$ <sub>42</sub> only was 115.7 pg/ml. The measured A $\beta$ <sub>42</sub> of another sample contained both A $\beta$ <sub>42</sub> and A $\beta$ <sub>40</sub> was quantified to be 104.6 pg/ml. The recovery rate of measured A $\beta$ <sub>42</sub> by IMR between with and without A $\beta$ <sub>40</sub> is 90.4% with a error range less than 10%.

Human plasma contains various and abundant endogenous biomolecules may interfere the measurement of IMR assay on plasma A $\beta$ <sub>42</sub>. The chemicals in medicine used to treatment inflammatory diseases, viral and bacterial infections, cardiovascular disease and Alzheimer's disease may also interfere. Each of these common molecules and chemicals (10,000 mg/ml of hemoglobin, 600 mg/ml of conjugated bilirubin, 30,000 mg/ml of intra lipid, 200 mg/ml of uric acid, 500 IU/ml of rheumatoid factor, 60,000 mg/ml of albumin, 500 mg/ml of acetylsalicylic acid, 300 mg/ml of ascorbic acid, 1,000 mg/ml of ampicillin sodium, 100 ng/ml of Quetiapine Fumarate, 90 ng/ml of Galanthamine hydrobromide, 100 ng/ml of Rivastigmine hydrogen tartrate, 1,000 ng/ml of Donepezil Hydrochloride and 150 ng/ml of Memantine Hydrochloride) are spiked in same plasma sample contains 115.7 pg/ml A $\beta$ <sub>42</sub> quantified by IMR assay, separately. The measured plasma A $\beta$ <sub>42</sub> ranges from 104.3 pg/ml to 123.8 pg/ml, and the corresponding recovery rate of measured A $\beta$ <sub>42</sub> by IMR between with and without interfering materials is within 90.1% to 107.0% with a error range less than 10%. Taken together, this finding indicates that the A $\beta$ <sub>40</sub>, biomolecules, drugs and chemicals listed above do not interfere with the assay of plasma A $\beta$ <sub>42</sub> by IMR.

In order to validate the dilution linearity of assaying A $\beta$ <sub>42</sub> by IMR, a dilution recovery study was performed by diluting a plasma sample containing A $\beta$ <sub>42</sub> by factors



of 5, 10, 20, 50 and 100 with PBS buffer. The measured A $\beta$ <sub>42</sub> concentration of the original sample (un-diluted) is 1059.43 pg/ml spiked with synthetic A $\beta$ <sub>42</sub> in plasma. The dilution recoveries for samples diluted 1:5, 1:10, 1:20, and 1:50 ranged from 97.2 % to 108.9 % with a error range less than 10%. The dilution recovery for sample diluted 1:100 was 115.3%. So, the highest linear dilution factor is 50 times.

The plasma A $\beta$ <sub>42</sub> levels assayed with IMR in AD at individual and combined cohorts were  $17.9 \pm 4.0$  pg/ml (GOT),  $17.9 \pm 3.9$  pg/ml (AMST), and  $17.9 \pm 4.3$  pg/ml (combined). In controls, the plasma A $\beta$ <sub>42</sub> levels assayed with IMR individual and combined sites were  $13.7 \pm 0.7$  pg/ml (GOT),  $16.8 \pm 1.8$  pg/ml (AMST), and  $15.5 \pm 2.1$  pg/ml (combined) for CONT. The AD group showed a higher level of plasma A $\beta$ <sub>42</sub> than the control group ( $p < 0.001$ ), as shown in Table 2. The increase in plasma A $\beta$ <sub>42</sub> level in AD patients of these European cohorts assayed with IMR is consistent with Taiwan and US studies [18-20]. According to the results in Table 2, the ratio of A $\beta$ <sub>42</sub> level in plasma to that in CSF was approximately 1.6% for controls and 4.1% for AD patients.

In Table 2, the opposite change in A $\beta$ <sub>42</sub> levels in CSF and plasma between controls and AD patients is evidenced. The relationship between CSF A $\beta$ <sub>42</sub> and plasma A $\beta$ <sub>42</sub> of the 106 subjects is plotted in Fig. 1, showing a non-linear correlation between CSF A $\beta$ <sub>42</sub> and plasma A $\beta$ <sub>42</sub>. Spearman correlations are used to analysis the CSF-Plasma A $\beta$ <sub>42</sub> correlations in controls and in AD, separately. In controls, there was a weakly positive correlation between CSF A $\beta$ <sub>42</sub> and plasma A $\beta$ <sub>42</sub> levels ( $r = 0.186$ ). However, in AD, there is a moderately negative correlation between CSF A $\beta$ <sub>42</sub> and plasma A $\beta$ <sub>42</sub> levels ( $r = -0.352$ ). This points out that the plasma A $\beta$ <sub>42</sub> level dramatically increases with the decreasing CSF A $\beta$ <sub>42</sub> level in AD.

By combining the control and AD groups, all data points in Figure 1 are fitted to hyperbolic curve:

$$\text{Plasma } A\beta_{42} = \alpha \frac{\text{CSF } A\beta_{42}}{\text{CSF } A\beta_{42} - \varphi}, \quad (1)$$

where  $\alpha$  and  $\varphi$  are fitting parameters. By fitting the data to Eq. (1), the parameters are obtained to be 12.1 and 130.4, respectively. The fitting curve is plotted with the solid line in Fig. 1. The meanings of  $\alpha$  and  $\varphi$  in Eq. (1) are the low-limited values of plasma  $A\beta_{42}$  and CSF  $A\beta_{42}$  levels respectively, as plotted with dashed lines in Fig. 1.

## DISCUSSION

To our knowledge, this is the first report showing that plasma  $A\beta_{42}$  levels are negatively correlated with CSF  $A\beta_{42}$  levels in AD patients. In contrast, a previous study recently reported both plasma and CSF  $A\beta_{42}$  levels dropped in the dementia stage when assayed using ultrasensitive digital ELISA methodology (Simoa assay) [12]. This means  $A\beta_{42}$  level in plasma and in CSF assayed with Simoa showed a slightly positive correlation. The opposite finding of an inverse (negative) correlation between CSF and plasma  $A\beta_{42}$  in the current study might be related to the different designs of technological platforms used. The Simoa method [12] is based on the sandwich assay and thus relies on the binding of two antibodies (capture and detection antibody) to measure  $A\beta_{42}$  molecules in body fluids [12,28], with the first antibody used to capture the N-terminal of  $A\beta_{42}$ , whereas the second antibody binds to the C-terminal domain of  $A\beta$ . Because plasma  $A\beta_{42}$  is frequently bound to carrier proteins in blood, such as albumin or lipoproteins [29], this may induce a potential stereoscopically obstacle for two antibodies to associate with one  $A\beta_{42}$  molecule simultaneously, with loss of some plasma  $A\beta_{42}$  signal by using two antibodies in

sandwich method. In contrast, the IMR method is a single-antibody immunoassay. The antibody specifically capturing C-terminal (a.a. 37-42) of A $\beta$ <sub>42</sub> is anchored on the magnetic nanoparticles to detect A $\beta$ <sub>42</sub> molecule. Based on the design of IMR assay, it ideally has a higher possibility to capture and detect A $\beta$ <sub>42</sub> molecule when C-terminal of A $\beta$ <sub>42</sub> is exposed in various conformations, such as isolated, complex or oligomeric form. This may explain the different signal for IMR in comparison with the sandwich-based immunoassay when detecting A $\beta$ <sub>42</sub>. Another explanation for the differing results is that the antibody used in the IMR experiments is a polyclonal antibody that has been reported to react with several 25-85 kDa bands of unknown identity at western blot of human plasma according to the commercial vendor. It was evidenced that IMR A $\beta$ <sub>42</sub> assay is specific for A $\beta$ <sub>42</sub> in the presence of A $\beta$ <sub>40</sub> in present study. Whether these are made up from oligomerised A $\beta$ <sub>42</sub> or other anti-A $\beta$ -reactive proteins remains to be examined.

In addition to assay methodologies, we propose the following hypothesis from the biology point of view to explain the observed negative correlation between plasma A $\beta$ <sub>42</sub> and CSF A $\beta$ <sub>42</sub> levels in this study. CSF A $\beta$ <sub>42</sub> shows a significant reduction in AD patients as reported in many studies [5-9], probably caused by aggregation and deposition of A $\beta$ <sub>42</sub> in brain or a defect of A $\beta$ <sub>42</sub> clearance which leads to lower amount of A $\beta$ <sub>42</sub> molecules transport to CSF[30]. In contrast, when plasma A $\beta$ <sub>42</sub> levels are measured by the IMR technique, there is an increase in AD [18, 20-22], probably related to the different transportation systems to move A $\beta$ <sub>42</sub> from the brain to the CSF and to move A $\beta$ <sub>42</sub> from the brain to the peripheral blood. Following is our hypothesis to emphasize the impact of independent transportation system on increasing plasma A $\beta$ <sub>42</sub> levels in AD.

It is known that some clearance systems exist for transportation of A $\beta$ <sub>42</sub> from brain to peripheral blood in order to clean out toxic A $\beta$ <sub>42</sub> [31]. The blood-brain barrier (BBB) could play a role as a barrier to allow transportation of monomeric and soluble forms of A $\beta$ <sub>42</sub> to the peripheral blood. The ratio of A $\beta$ <sub>42</sub> in plasma as compared with CSF is small (< 5%; Table 2), a figure similar to a previous study [32], which may indicate that only small portion of A $\beta$ <sub>42</sub> born in brain can reach peripheral blood. But in AD, the clearance systems might keep working to transport more A $\beta$ <sub>42</sub> to peripheral blood to avoid more A $\beta$ <sub>42</sub> accumulating in brain. This may be one of the reasons that A $\beta$ <sub>42</sub> level increased in peripheral blood of AD patient in present study. An alternative explanation for the inverse correlation between plasma and CSF A $\beta$ <sub>42</sub> levels in AD patients is the difference in composition of the matrix. The total protein concentration in blood plasma is approximately 50-70 g/l for an adult. The blood plasma is abundant in albumin (which constitute 50-60% of blood plasma proteins) that may carry substantial amounts of A $\beta$ <sub>42</sub> [33] as compared with the amount of free A $\beta$ <sub>42</sub>. Because albumin is highly soluble in blood matrix, albumin-A $\beta$ <sub>42</sub> complexes may be more prone to stay in a soluble form, which may prevent A $\beta$ <sub>42</sub> from oligomerization and aggregation in blood. When A $\beta$ <sub>42</sub> is transported from brain to peripheral blood in AD, it is a logical that higher level of soluble A $\beta$ <sub>42</sub> in blood plasma are quantified by the IMR assay than by a sandwich immunoassay. On the other hand, the total protein level in spinal fluid is less than 1% of that in plasma, with albumin levels around 230 mg/l as compared to 40 g/l in plasma [34]. In this environment with low levels of carrier proteins, aggregation-prone A $\beta$ <sub>42</sub> molecules may relatively more easily contact with each other to form insoluble aggregates, which could reduce levels quantified by conventional sandwich immunoassays. On the contrast, IMR assay shows better

sensitivity and consistence when quantifying ultra-low concentration of plasma A $\beta$ <sub>42</sub> from various and independent cohorts than conventional ELISA. In order to clarify the matrix effect of above interpretation, meanwhile to exclude the divergence between methodologies, a study of quantification of CSF A $\beta$ <sub>42</sub> and plasma A $\beta$ <sub>42</sub> by IMR assay form same subjects is necessary for further study.

## **CONCLUSION**

We demonstrate the correlation between plasma and CSF A $\beta$ <sub>42</sub> levels in two independent clinical cohorts. While CSF A $\beta$ <sub>42</sub> levels were measured using sandwich ELISA methods, plasma A $\beta$ <sub>42</sub> levels were measured with IMR, which is a technique based on a single antibody. A hyperbolic curve was found for the relationship between plasma A $\beta$ <sub>42</sub> and CSF A $\beta$ <sub>42</sub> in the whole set of samples. While plasma and CSF A $\beta$ <sub>42</sub> levels were weakly positive correlated in the control group, a moderately negative correlation between plasma and CSF A $\beta$ <sub>42</sub> levels was observed within the AD group. This negative correlation in AD presented in this study may be caused by the differences of assaying methodologies, A $\beta$ <sub>42</sub> transportation systems or matrix effect of blood and CSF.

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### **Caption**

Figure 1. Relationship between plasma  $A\beta_{42}$  and CSF  $A\beta_{42}$  levels for control (CONT) and AD group. The solid line denotes the hyperbolic function with two asymptotic lines plotted with the dashed lines.

Table 1. The demographic information and CSF A $\beta$ <sub>42</sub> level of subjects in this study.

Site	Group	Numbers	Age (yrs.)	Gender (Male %)	CSF A $\beta$ <sub>42</sub> (pg/ml) <sup>&amp;</sup>
Sahlgrenska University Hospital (GOT)	CONT <sup>*</sup>	18	71.6 ± 11.3	35.3%	901.3 ± 177.2
	AD <sup>#</sup>	33	80.7 ± 9.0	53.8%	402.2 ± 105.3
Amsterdam Dementia (AMST)	CONT	25	63.1 ± 5.6	32.0%	979.7 ± 190.6
	AD	30	60.4 ± 3.2	53.5%	465.2 ± 106.9

\*CONT: Control, #AD: Alzheimer's disease, &Mean ± SD

Table 2. Detected A $\beta$ <sub>42</sub> levels in CSF and plasma for subjects in CONT and AD groups.

Group	Numbers	CSF A $\beta$ <sub>42</sub> <sup>+</sup> (pg/ml)	Plasma A $\beta$ <sub>42</sub> <sup>++</sup> (pg/ml)	Ratio <sup>#</sup>
CONT	43	946.9 ± 187.1	15.5 ± 2.1	1.6%
AD	63	432.2 ± 109.9	17.9 ± 4.3	4.1%

Mean ± SD; <sup>+</sup>Detected using conventional ELISA; <sup>++</sup>Detected using

IMR; <sup>#</sup>A $\beta$ <sub>42</sub> level ratio of plasma to CSF.

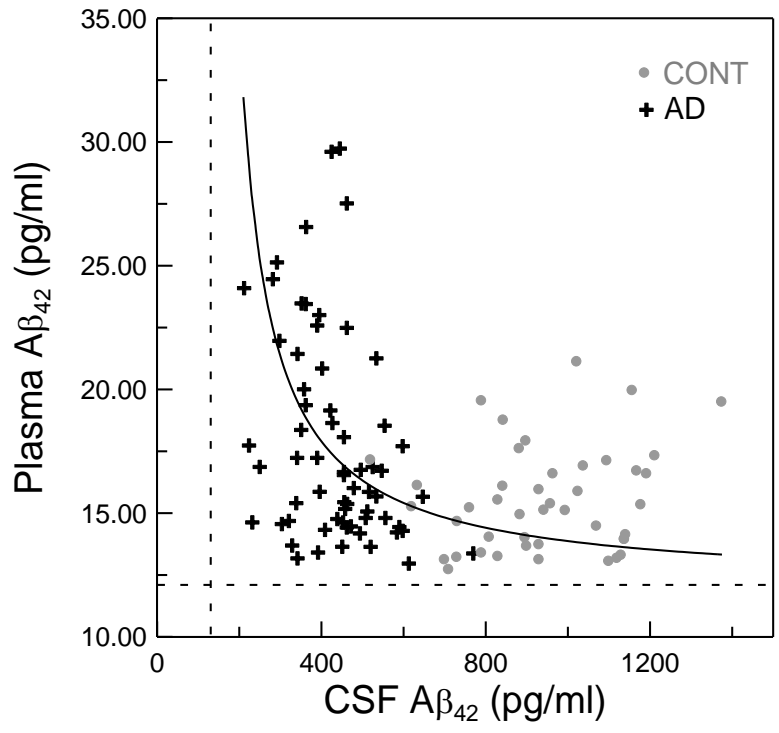


Fig. 1