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SHORT REPORT

The global Alzheimer's Association round robin study on plasma amyloid β methods

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Abstract

Introduction: Blood-based assays to measure brain amyloid beta (Aβ) deposition are an attractive alternative to the cerebrospinal fluid (CSF)–based assays currently used in clinical settings. In this study, we examined different blood-based assays to measure Aβ and how they compare among centers and assays.

Methods: Aliquots from 81 plasma samples were distributed to 10 participating centers. Seven immunological assays and four mass-spectrometric methods were used to measure plasma Aβ concentrations.

Results: Correlations were weak for Aβ42 while Aβ40 correlations were stronger. The ratio Aβ42/Aβ40 did not improve the correlations and showed weak correlations.

Discussion: The poor correlations for Aβ42 in plasma might have several potential explanations, such as the high levels of plasma proteins (compared to CSF), sensitivity to pre-analytical sample handling and specificity, and cross-reactivity of different antibodies. Different methods might also measure different pools of plasma Aβ42. We, however, hypothesize that greater correlations might be seen in future studies because many of the methods have been refined during completion of this study.

KEYWORDS
Alzheimer's disease, amyloid beta, biomarkers, method comparison, plasma

1 | INTRODUCTION

In Alzheimer's disease (AD), amyloid beta (Aβ) deposition in the brain is detectable using the cerebrospinal fluid (CSF) biomarkers Aβ42 or Aβ42/40 ratio and by using amyloid positron emission tomography (PET).[1] Because CSF sampling is mainly performed at memory clinics and other specialized centers and amyloid PET is costly with limited availability, blood-based assays have long been an attractive alternative, especially in the primary care setting. The ability to reliably distinguish AD dementia from controls using Aβ in plasma has until 2016 showed poor performance and partially conflicting results.[2] However, newly developed highly sensitive immunoassays, as well as mass spectrometry (MS) methods, have shown a better and higher concordance of Aβ in plasma with Aβ-PET or CSF amyloid status.[3–7]

The aim of this study was to examine how different methods that measure plasma Aβ42 and Aβ40 levels compare, and whether results correlate linearly. Ten centers participated in this study, which included seven immunoassays and four MS methods, each analyzing aliquots of 81 unique ethylenediaminetetraacetic acid (EDTA)–plasma samples.

2 | METHODS

Individual de-identified EDTA–plasma samples (n = 81) were measured from the prospective and longitudinal Swedish BioFINDER (Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably) cohort (n = 48); the prospective University College London Dementia Research Centre CSF cohort (n = 24); and the Clinical Neurochemistry Laboratory at the Sahlgrenska University Hospital, Mölndal, Sweden (n = 9). Varied sampling and processing procedures were used across these centers, and for this study the samples were prepared in 250 μL aliquots, so each underwent one freeze–thaw cycle prior to distribution. These aliquots were kept at −80°C pending distribution to participating centers. The plasma samples were selected based on known matched CSF Aβ42 concentrations previously measured in the original cohorts, to theoretically include samples with a wide range of plasma Aβ levels. Across the 10 participating centers (Table 1), seven immunological assays and four MS methods were used in this study. All methods measured Aβ40 and Aβ42 but varied in whether the full-length Aβ1-40 and Aβ1-42 forms were measured (for simplicity, the terms Aβ40 and Aβ42 are used throughout), and two methods also measured the $APP_{669\text{-}711}$ form. Methods were compared using Passing-Bablok regression[8] and Spearman's rank correlation coefficient (r_s).

3 | RESULTS

The correlations for pair-wise method comparison (Figure 1) for Aβ42 were generally weak to moderate with a median r_s value of 0.24 and highest r_s value of 0.72. The correlations for Aβ40 were stronger with a median r_s value of 0.67 and highest r_s value of 0.89. Interestingly, using the ratio Aβ42/Aβ40 did not improve the correlations (Figure 2) and showed weak correlations (similar to Aβ42) with a median r_s value of 0.25 and highest r_s value of 0.65. See supporting information for full correlation plots between all methods for Aβ40, Aβ42, and the Aβ42/Aβ40 ratio.

4 | DISCUSSION

The results in this multicenter study showed acceptable correlations for plasma Aβ40, while there were poor correlations for plasma Aβ42, as well as for the Aβ42/Aβ40 ratio. The moderate correlations between the MS assays support comparable measurements but correlations are not ideal (generally < 0.7).

The MagQu method, which uses one antibody to capture Aβ40 and Aβ42 and immunomagnetic reduction to quantify the protein, does not correlate with the other methods, thus it may measure other forms of

TABLE 1 Participating centers, assay platform, and measured Aβ species

Center	Technology platform	Aβ species	Capture antibody	Detection antibody	Calibrant
University of Pennsylvania Biomarker Research Lab	Simoa (commercial)	Aβ42 Aβ40	H31L21 12F4	6E10 6E10	AnaSpec #24236 & #20276
ADx/Euroimmun	ELISA	Aβ1-42 Aβ1-40	21F12 2G3	3D6 3D6	rPeptide rPeptide
Amsterdam UMC/ADx	Simoa (in-house) (Amyblood)	Aβ1-42 Aβ1-40	21F12 2G3	3D6 3D6	rPeptide rPeptide
Araclon Biotech	ELISA (ABtest)	Aβ1-42 Aβ1-40 and N-truncated species up to N3pE-42	1F3 (Araclon Biotech)	pAB031 and pAB002 (Araclon Biotech)	Synthetic Aβ1-40 and Aβ1-42 peptides (Araclon Biotech)
Araclon Biotech	LC-MS	Aβ1-42 Aβ1-40	None	None	rPeptide Uniformly labeled 15N, recombinant
Shimadzu Corporation	MALDI-TOF MS	Aβ1-42 Aβ1-40 APP669-711	6E10 (BioLegend)	None	AnaSpec AnaSpec PEPTIDE INSTITUTE
MagQu Taiwan	IMR	Aβ42 Aβ40	Abcam (ab34376) BAM-10	None	rPeptide
Roche Diagnostics	Elecsys	Aβ1-42 Aβ1-40	21F12 & 23C2	3D6	Synthetic peptide in artificial matrix
University of Gothenburg	IP-LC-MS	Aβ1-42 Aβ1-40 APP669-711	Biolegend Aβ, 17-24 (4G8) & 1-16 (6E10)	None	rPeptide Uniformly labeled 15N, recombinant
Washington University	IP-LC-MS	Aβ42 Aβ40	HJ5.1	None	rPeptide Uniformly labeled 15N, recombinant
Eli Lilly	Simoa (in-house)	Aβ1-42 Aβ1-40	3D6	2G3—Aβ1-40 21F12—Aβ1-42	Eli Lilly reference standard

Abbreviations: Aβ, amyloid β; ADNI, Alzheimer's Disease Neuroimaging Initiative; ELISA, enzyme-linked immunosorbent assay; IMR, ImmunoMagnetic Reduction; IP-LC-MS, immunoprecipitation (IP) coupled to liquid chromatography mass spectrometry (LC-MS); MALDI-TOF-MS, matrix-assisted laser desorption–ionization-time of flight mass spectrometry; Simoa, single molecule array.

FIGURE 1 Amyloid beta (Aβ)1-40 (top), Aβ1-42 (middle), and Aβ1-42/Aβ1-40 (bottom) correlations (Spearman) between the different centers and methods

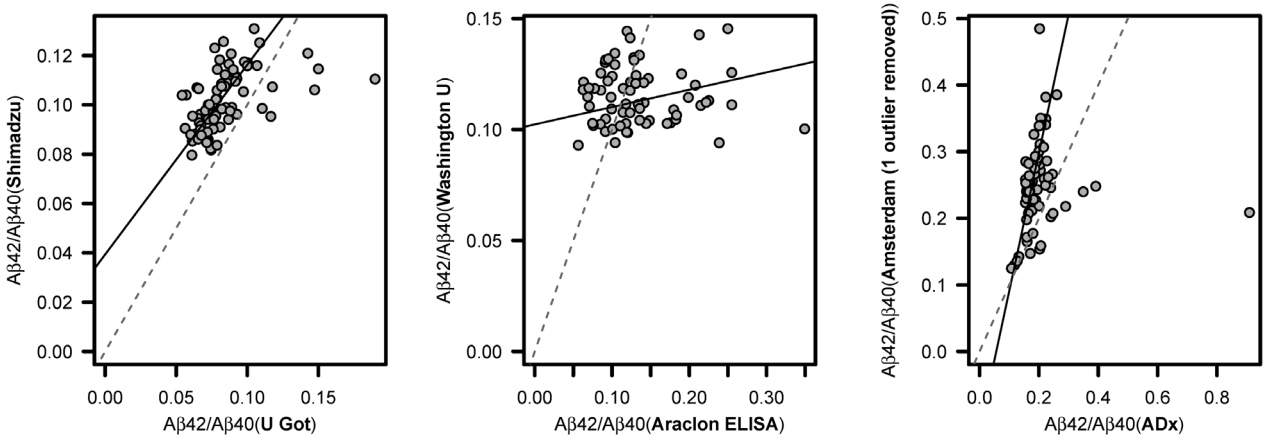

FIGURE 2 Examples of amyloid beta (Aβ)1-42/Aβ1-40 correlation plots between different centers. The solid line represents the Passing-Bablok regression line and the dashed line denotes the unity line (y = x). See supporting information for complete set of plots for all centers

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using PubMed and conference presentations. While blood-based assays until recently have shown conflicting results in the ability to distinguish Alzheimer's disease from controls compared to cerebrospinal fluid (CSF) biomarker profiles (amyloid beta [Aβ] and tau) and amyloid positron emission tomography (PET), newly developed methods to measure Aβ in plasma have shown results with improved diagnostic performance for specific applications. Citations directly relevant to the included assays and their contexts are cited.
2. Interpretation: The findings in this study show correlations among 11 methods that measured ethylenediaminetetraacetic acid–plasma Aβ42 and Aβ40. Further standardization, qualification, and validation work is needed to obtain a more harmonized outcome among detection methods.
3. Future directions: Since completion of this study, many of the methods have undergone additional refinement by the vendors. Future method comparison studies will show if this will result in higher correlations between the methods or improved clinical performance; if not, an in-depth analysis of method differences needs to be undertaken.

Aβ, which might explain the increased (not decreased) levels of Aβ42 and Aβ42/Aβ40 ratio in plasma of AD patients compared to controls.[9] Based on previous studies, this method may require special sample preparation procedures to obtain consistent results.[10]

There might be several potential explanations for the discrepancies between the measurements obtained by the different methods used in this study. First, plasma is a much more complex matrix compared to CSF, with very high levels of albumin, immunoglobulin G, and other plasma proteins (approximately 200 times higher in plasma than in CSF), and also lipoprotein particles containing apolipoprotein E (apoE) and other apolipoproteins that may form complexes with Aβ. This makes plasma a difficult matrix for Aβ measurements. These proteins may block the binding of antibodies to their respective analytes in the assays. In contrast, CSF has a less complicated matrix, and round robin studies on CSF Aβ42 and Aβ40 show very tight correlations across different assays, with a median correlation coefficient of 0.98.[11] It is also possible that different methods measure different pools of plasma Aβ42 but these may still show diagnostic utility as reported by different groups[12,13] and, as exemplified also by the inverse correlations for the MagQu assay. Different methods might also be differentially sensitive to method-specific pre-analytical sample handling in the local analysis laboratories, which might have been different in the originating cohorts, but aliquots distributed to the different centers were identical in the present study. Specificity of the used antibodies, cross-reactivity with other Aß isoforms, sample dilution before analysis, additive,s and pre-incubation procedures are other factors that might influence the sensitivities. In addition, Aβ42 concentrations are still at or close to the lower limit of quantification of most methods in plasma samples, which also may explain the higher correlations between assays for the more abundant Aβ40 compared to Aβ42. Furthermore, several studies reported similar findings comparing enzyme-linked immunosorbent assays and Simoa platforms for plasma Aβ40 and Aβ42.[7,14,15] Spearman coefficients were 0.68 and 0.71 for, respectively, Aβ40 and Aβ42, which corroborates the findings in this article for the same assays. Since completion of this study, many of the methods have undergone additional refinement and new method comparison studies are underway. We hypothesize that greater correlations will now be seen; if not, an in-depth analysis of method differences will need to be undertaken.

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CONFLICTS OF INTEREST

OH has acquired research support (for the institution) from Avid Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Alzpath, Biogen, Cerveau, and Roche. SP is a full-time employee of Roche Diagnostics GmbH and holds shares in Roche. TB is a full-time employee of and owns stock in F. Hoffmann-La Roche Ltd. KB has served as a consultant, on advisory boards, or on data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. HZ has served on scientific advisory boards for Alector, Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies and CogRx. JLD is an employee and stockholder of Eli Lilly and Company. ELECSYS is a trademark of Roche. E Stoops and KM are full-time paid employees of ADx NeuroSciences. JMS has received research funding from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly and Company); has consulted for Roche Pharmaceuticals, Biogen, Merck, and Eli Lilly; given educational lectures sponsored by GE Healthcare, Eli Lilly, and Biogen; and serves on a Data Safety Monitoring Committee for Axon Neuroscience SE. RJB cofounded C2N Diagnostics. Washington University and Dr. Bateman have equity ownership interest in C2N Diagnostics and receive royalty income based on technology (stable isotope labeling kinetics and blood plasma assay) licensed by Washington University to C2N Diagnostics. He receives income from C2N Diagnostics for serving on the scientific advisory board. Washington University, with RJB as co-inventor, has submitted the US provisional patent application "Plasma Based Methods for Detecting CNS Amyloid Deposition." He has received consultant fees from Roche, C2N Diagnostics, Genentech, AbbVie, Pfizer, Boehringer-Ingelheim, Eisai, AC Immune, Janssen, and Merck. He serves as principal investigator of the DIAN-TU, which is supported by the Alzheimer's Association, GHR Foundation, Eisai, an anonymous organization ,and the DIAN-TU

Pharma Consortium. HV is a founder of Biomarkable and a co-founder of ADx NeuroSciences. RY and NK are full-time employees of Shimadzu Corporation. NK holds stock in Shimadzu Corporation and has received payment for manuscript writing from Rinshohoushasen. CET has a collaboration contract with ADx Neurosciences and Quanterix; performed contract research or received grants from AC-Immune, Axon Neurosciences, Biogen, Brainstorm Therapeutics, Celgene, EIP Pharma, Eisai, PeopleBio, Roche, Toyama, Vivoryon; received honoraria from Medidact Neurologie. LMS has received honorarium from Biogen for teaching. LS and JA have submitted patents for "Methods for quantification of amyloid beta peptides in plasma by mass spectrometry." AN received honoraria from The Educational Program for Dementia Experts in Hokuriku (NINPRO), The Japan Society for the Promotion of Science (JSPS), Translational Research Center for Medical Innovation (TRI), Eisai Co. Ltd. SY is an employee and shareholder of MagQu Co., Ltd. KGM, VO, and JB have submitted patent application "Plasma Based Methods for Detecting CNS Amyloid Deposition" and may receive royalties based on blood plasma assay technology licensed to C2N Diagnostics. ES has received payment (to institution) from Roche Diagnostics for medical writing.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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