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► To cite this version:

Olivier Hanon, Jean-Sébastien Vidal, Sylvain Lehmann, Stéphanie Bombois, Bernadette Allinquant, et al.. Plasma amyloid levels within the Alzheimer's process and correlations with central biomarkers. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 2018, 14 (7), pp.858-868. 10.1016/j.jalz.2018.01.004 . hal-02533144

HAL Id: hal-02533144

<https://hal.univ-lorraine.fr/hal-02533144v1>

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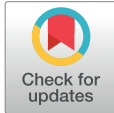
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ELSEVIER



Alzheimer's & Dementia 14 (2018) 858-868

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Featured Article

Plasma amyloid levels within the Alzheimer's process and correlations with central biomarkers

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The authors have declared that no conflict of interest exists.

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<https://doi.org/10.1016/j.jalz.2018.01.004>

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Abstract

Introduction: Diagnostic relevance of plasma amyloid β ($A\beta$) for Alzheimer's disease (AD) process yields conflicting results. The objective of the study was to assess plasma levels of $A\beta_{42}$ and $A\beta_{40}$ in amnesic mild cognitive impairment (MCI), nonamnesic MCI, and AD patients and to investigate relationships between peripheral and central biomarkers.

Methods: One thousand forty participants (417 amnesic MCI, 122 nonamnesic MCI, and 501 AD) from the Biomarker of Amyloid peptide and Alzheimer's disease Risk multicenter prospective study with cognition, plasma, cerebrospinal fluid (CSF), and magnetic resonance imaging assessments were included.

Results: Plasma $A\beta_{1-42}$ and $A\beta_{1-40}$ were lower in AD (36.9 [11.7] and 263 [80] pg/mL) than in amnesic MCI (38.2 [11.9] and 269 [68] pg/mL) than in nonamnesic MCI (39.7 [10.5] and 272 [52] pg/mL), respectively ($P = .01$ for overall difference between groups for $A\beta_{1-42}$ and $P = .04$ for $A\beta_{1-40}$). Globally, plasma $A\beta_{1-42}$ correlated with age, Mini-Mental State Examination, and *APOE* $\epsilon 4$ allele. Plasma $A\beta_{1-42}$ correlated with all CSF biomarkers in MCI but only with CSF $A\beta_{42}$ in AD.

Discussion: Plasma $A\beta$ was associated with cognitive status and CSF biomarkers, suggesting the interest of plasma amyloid biomarkers for diagnosis purpose.

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Keywords:

Alzheimer's disease; Mild cognitive impairment; CSF biomarkers; Amyloid β peptides; Plasma biomarkers; Dementia; Cohort study

1. Introduction

Alzheimer's disease (AD) is preceded by a very long pre-symptomatic or prodromal phase. Biomarkers able to detect the in vivo changes of the amyloid β ($A\beta$) peptides, and tau proteins improve diagnosis and detection of at-AD-risk subjects. Among these biomarkers, cerebrospinal fluid (CSF) $A\beta_{42}$, tau, phosphorylated tau (p-Tau), and cortical amyloid-positron emission tomography (PET) scans have been included in the International Guidelines for AD diagnosis in clinical research settings [1]. CSF $A\beta_{42}$ is reduced at least 15 years before symptoms' onset [2], and the relevance of CSF amyloid has been confirmed for positive [3], differential [4], and early phases (mild cognitive impairment [MCI] and prodromal AD) [5]. A strong correlation is observed between CSF $A\beta_{42}$ and cortical amyloid-PET in AD. Lumbar puncture remains an invasive technique, and amyloid-PET is still expensive and not a screening tool. This highlighted the need of less invasive and expensive biomarkers that could predict central amyloid status. The most promising biomarker seems to be the plasma $A\beta_{42}$, although previous studies have controversial results. Elderly nondemented participants with a higher plasma $A\beta_{42}$ level and a lower plasma $A\beta_{42}/A\beta_{40}$ ratio at baseline have an increased risk of dementia [6]. A decrease of plasma $A\beta_{42}$ level is associated with the progression from controls and MCI to AD [7]. Others studies yield conflicting results regarding the predictive value of plasma $A\beta_{42}$ for AD diagnosis and for cognitive

decline in at-AD-risk population [4,6,8–19]; meanwhile, the combination of plasma $A\beta_{42}$ levels and others biomarkers might improve the predictive value [14,20]. Recently, innovative technique allows the quantification of amyloid in plasma with complex proteomics techniques, so far hardly implementable in routine [21]. Although discrepancies between studies can be explained by many factors, the missing link remains the understanding of the relationship between peripheral and central biomarkers at early stage of the disease.

Therefore, the aim of this study was (1) to assess the plasma levels of amyloid $A\beta_{1-42}$ and $A\beta_{1-40}$ in a large clinically based cohort of amnesic MCI (aMCI), nonamnesic MCI (naMCI), and AD patients and (2) to investigate the relationships between plasma $A\beta_{1-42}$, $A\beta_{1-40}$, CSF, and brain imaging biomarkers in a large prospective cohort taking into account potential confounding factors.

2. Methods

2.1. Study population

BALTAZAR (Biomarker of Amyloid peptide and Alzheimer's disease Risk) is a multicenter (23 memory centers) prospective cohort study (ClinicalTrials.gov Identifier #NCT01315639) including participants with MCI or AD at baseline from September 2010 to April 2015 and with an ongoing 3-year follow-up. All participants were Caucasian, community-dwellers and had caregivers. Inclusion criteria

for AD participants were age ≥ 45 years, probable AD based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [22], and from mild to moderate stage (Mini-Mental State Examination [MMSE] score > 15). Inclusion criteria for MCI participants were age ≥ 70 years with MCI diagnostic criteria according to Petersen [23]. Exclusion criteria were non-AD dementia (i.e., vascular dementia, Lewy body or Parkinson dementia, and frontotemporal dementia); genetic forms of AD; major depression according to DSM IV-TR or geriatric depression scale (GDS $> 20/30$); other diseases that could interfere with cognitive evaluation; diseases with short-term survival; use of cholinesterase inhibitors or methyl-D-aspartate receptor partial antagonists before the inclusion (for MCI participants); and illiterateness or less than 4 years of education.

At baseline, all the participants underwent clinical, neuropsychological, and biological assessments, and participants without contraindications underwent magnetic resonance imaging (MRI) brain examinations. Cognitive evaluations were performed by neuropsychologists after training program to harmonize the quotation. MCI participants underwent the neuropsychological test battery that included global evaluation with the MMSE, visual recognition memory task (DMS48), free and cued selective recall reminding test (16 items), verbal fluency tests, trail making tests A and B, digit symbol substitution test, clock test, motor planning tests, and the picture-naming test (DO80). MCI participants were then categorized as amnesic or nonamnesic according to the presence of memory impairment on the free and cued selective recall reminding test related to age, sex, and educational level. AD participants underwent cognitive evaluations that consisted of Alzheimer's Disease Assessment Scale–Cognitive Subscale, clock test, verbal fluency tests, and Clinical Dementia Rating Scale.

To follow more recent diagnostic criteria [24], we reclassified MCI participants in MCI core-clinical, MCI low-likelihood, MCI intermediate-likelihood, and MCI high-likelihood groups, based on the positivity of amyloid and neuronal injury biomarkers such as CSF A β_{42} for amyloid biomarkers and CSF tau or the presence of an MRI hippocampal atrophy for neuronal injury.

All participants or their legal guardians gave written informed consent. The study was approved by the Paris Ethics Committee (CPP Ile de France IV Saint Louis Hospital).

2.2. Plasma and CSF sampling and analysis

Blood and CSF samples were collected on the same day and time of the day. People involved in biological analysis were blinded to other assessments. A standard protocol was established beforehand and used throughout the study. All centers used the same 10 mL collection tube with EDTA (BD Vacutainer K2E ref 367,525; Becton Dickinson,

USA). After centrifugation (2500 g, 10 minutes), supernatant liquid was aliquoted in polypropylene protein low-binding tubes (LoBind-microtube-ref 022431064; Eppendorf, Hamburg, Germany) and stored at -80°C . Biomarker measurements were performed in a single centralized laboratory (UMRS1172 former INSERM U837; Lille, France). Plasma A β peptide assay was performed using the INNO-BIA kit (Fujirebio Europe NV, formerly Innogenetics NV, Belgium), based on a multiplex xMAP technique with a LABScan-200 system (Luminex BV, The Netherlands). A β peptide levels from each blood draw were measured in duplicate using the same aliquot.

Lumbar CSF samples were collected according to a standardized protocol [25,26]. CSF samples (> 4 mL) were centrifuged (1000 g, $+4^{\circ}\text{C}$, 10 minutes) less than 4 hours after collection using the same 10 mL polypropylene tube (ref62.610.201; Sarstedt, Germany) and aliquoted into polypropylene protein low-binding tubes (LoBind microtube-ref 022431064; Eppendorf) and stored at -80°C . CSF A β_{42} , total-tau, and p-Tau $_{181\text{P}}$ levels were measured in duplicate using the same aliquot in a single centralized laboratory (IRMB, Montpellier, France) using commercially available Innostest sandwich ELISA INNOTEST hTAU Ag, INNOTEST β Amyloid $_{(1-42)}$, and INNOTEST Phospho-tau $_{(181\text{P})}$ according to the manufacturer's procedures (Fujirebio Europe N.V., Belgium). Owing to procedure's constraints, concentrations of total-tau above the detection limit (> 1200 pg/mL) were not recalculated after dilution.

2.3. MRI examination

The MRI protocol included a three-dimensional volumetric T1-weighted, an axial fluid-attenuated inversion recovery T2-weighted, an axial gradient echo T2-weighted, and an axial T2-weighted fast spin echo with slices angled parallel to axis through the genu and splenium of the corpus callosum and taken from foramen magnum to vertex. The protocol also included an axial blood-oxygen-level dependent echo planar imaging (10 minutes resting state), an axial diffusion tensor imaging (b-factor = 1000 s/mm 2 ; 32 directions). After MRI, the scans were sent for quality validation and postprocessing. MRI analysis was centralized and analyzed by the Centre d'acquisition et de traitement d'images [27]. Right and left hippocampal volumes were obtained for each participant using automatic segmentation of the hippocampus [28].

2.4. Potential confounding and moderating variables

The standardized interview included questions on demographic and socioeconomic characteristics, health status, and medication use. Cerebrovascular and cardiovascular diseases were defined as self-reported history of stroke and cardiovascular events; diabetes as a self-reported diagnosis of diabetes or fasting blood glucose > 7.0 mmol/L or use of glucose-modifying medication; dyslipidemia, smoking

habits defined as never, former, or current; or hypertension defined as a measured systolic blood pressure ≥ 140 mm Hg or diastolic ≥ 90 mm Hg or current use of antihypertensive treatment. Each participant had a physical examination performed by a physician with calculation of the body mass index (BMI) and Mini Nutritional Assessment. Functional disability was assessed using activities of daily living (normal score 6/6) and instrumental activities of daily living (normal score 14/14) scales. Depressive symptoms were evaluated with the GDS.

Apolipoprotein E (*APOE*) was genotyped in a single centralized laboratory (Centre de Biologie-Pathologie, Lille University Hospital, France) using a classical polymerase chain reaction and digestion method.

2.5. Statistical analysis

General characteristics were analyzed in the whole sample and according to AD, aMCI, or naMCI diagnosis. Categorical variables are presented as percentage and number of subjects [% (N)], continuous variables as mean and standard deviation [M (SD)], and comparisons were made with χ^2 or analysis of variance. Means levels of plasma and CSF biomarkers were calculated in the three groups and compared first with generalized linear regression with and without adjusted for age, sex, education level, and number of *APOE* $\epsilon 4$ allele with biomarkers as dependent variables and diagnosis treated nominally and ordinally (coded in the following order AD, aMCI, and naMCI) to assess a linear relationship. The models were further adjusted for systolic blood pressure, BMI, diabetes, history of stroke or transient ischemic attack, and dyslipidemia. Because all biomarkers had a skewed distribution, they were log-transformed for statistical testing; but for the sake of clarity, non-log-transformed biomarker means and standard deviations are presented. We performed a sensitivity analysis excluding AD patients aged ≤ 70 years ($n = 69$, 13.7%) to exclude early-onset AD that could carry presenile PS1 and PS2 mutations that may be associated with different forms of β amyloid. Relationships between CSF and plasma biomarkers were assessed in the whole sample and among AD, aMCI, and naMCI patients separately with Pearson correlation coefficients and with general linear regression models with plasma biomarkers as dependent variables and CSF biomarkers as independent variables adjusted for variables associated with plasma biomarkers (age and presence of *APOE* $\epsilon 4$ allele) and sex. Because of the small number of naMCI patients, we also analyzed correlation in the MCI group as a whole. Results of correlations of the plasma $A\beta_{1-42}$ and the CSF biomarkers are presented in scatter plots with regression and 95% confidence interval lines. Pearson correlation coefficients between plasma biomarkers and age, MMSE, and hippocampal volume were calculated. The same analyses were performed after reclassification of participants as per Albert' criteria [24]. Statistical analysis was performed using the R statistical software. In all analyses, the two-sided α -level of 0.05 was used for significance testing.

3. Results

3.1. Demographical, clinical, and MRI characteristics

One thousand forty participants were included (501 AD, 417 aMCI, and 122 naMCI) (Table 1, Fig. 1). There were more women in the naMCI group ($P = .004$). Educational level differed between groups ($P < .0001$). No between-group difference for age, smoking status, BMI, comorbidities, or GDS was observed. AD and aMCI carried more often *APOE* $\epsilon 4$ allele ($P < .0001$) and had a lower MMSE score compared to naMCI participants ($P < .0001$). The activities of daily living and instrumental activities of daily living scores were lower in AD than in aMCI and naMCI participants. Among the MCI participants, the free and cued selective recall reminding test score was lower in aMCI than naMCI participants. All cognitive assessments were different between both groups except motor planning (Supplementary Table 1). Hippocampal volume measured in 837 participants was different between AD, aMCI, and naMCI ($P < .0001$) and between aMCI and naMCI ($P < .0001$).

3.2. Plasma and CSF biomarker characteristics

The levels of plasma $A\beta_{1-42}$ and $A\beta_{1-40}$ were lower in AD than in aMCI, than in the naMCI participants (for $A\beta_{1-42}$ [pg/mL]: 36.9 [11.7] in AD, 38.2 [11.9] in aMCI, and 39.7 [10.5] in naMCI [$P = .01$ in a model adjusted for age, sex, educational level, presence of *APOE* $\epsilon 4$ allele]; for $A\beta_{1-40}$ [pg/mL]: 263 [80] in AD, 269 [68] in aMCI, and 272 [52] in naMCI [$P = .04$]). When cognitive status (AD, aMCI, and naMCI) was treated nominally, the associations between cognitive status and plasma $A\beta_{1-42}$ and $A\beta_{1-40}$ were still significant ($P = .05$ and $P = .02$, respectively). When the model was adjusted for age, sex, and cardiovascular comorbidities (history of stroke or transient ischemic attack, systolic blood pressure, BMI, diabetes, and dyslipidemia), the relation was still significant for $A\beta_{1-42}$ ($P = .04$) but not for $A\beta_{1-40}$ ($P = .47$). The $A\beta_{1-42}/A\beta_{1-40}$ ratio showed an opposite variation without reaching significance. A reduction of 3.7% from naMCI to aMCI and of 7.3% from naMCI to AD was found for plasma $A\beta_{1-42}$. For plasma $A\beta_{1-40}$, the percentage of reduction was lower (1.1% from naMCI to aMCI and 3.3% from naMCI to AD) (Table 2).

The sensitivity analysis excluding AD patients aged 70 years and younger showed the same significant associations between cognitive status and $A\beta_{1-42}$ ($P = .04$) and $A\beta_{1-40}$ ($P = .02$).

From naMCI to aMCI and to AD, CSF $A\beta_{42}$ levels were progressively lower and CSF tau, p-Tau, and p-Tau/ $A\beta_{1-42}$ ratio levels were progressively higher. For CSF $A\beta_{1-42}$, there was a 13.9% reduction from naMCI to aMCI and a 28.1% reduction from naMCI to AD. All the results were obtained after adjustment for age, sex, educational level, and *APOE* $\epsilon 4$ status.

Table 1
Demographical, clinical, and MRI characteristics of BALTAZAR population

Characteristics, % (N)	Whole sample	AD	aMCI	naMCI	<i>P</i> [‡]
	N = 1040	N = 501	N = 417	N = 122	
Age (years), M (SD)	77.5 (6.6)	77.3 (7.7)	77.7 (5.5)	77.9 (5.2)	.58
Women	58.2 (605)	56.9 (285)	55.6 (232) [†]	72.1 (88) [†]	.004
Educational level					<.0001
Primary	20.1 (207)	25.4 (125)	15.9 (66)	13.3 (16)	
Secondary	37.8 (389)	39.8 (196)	37.0 (154)	32.5 (39)	
High school diploma or above	42.1 (433)	34.9 (172)	47.1 (196)	54.2 (65)	
Tobacco					
Current	7.41 (73)	7.13 (34)	8.38 (33)	5.26 (6)	.70
Former	61.3 (604)	61.8 (295)	59.4 (234)	65.8 (75)	
Never	31.3 (308)	31.0 (148)	32.2 (127)	28.9 (33)	
BMI (kg/m ²), M (SD)	25.0 (3.9)	25.0 (4.2)	25.2 (3.7)	24.5 (3.7)	.30
APOE genotype					
No APOE ε4 allele	55.1 (510)	49.8 (200)	55.1 (222)	73.3 (88)	
1 APOE ε4 allele	38.6 (357)	42.3 (170)	39.0 (157)	25.0 (30)	<.0001
2 APOE ε4 alleles	6.27 (58)	7.96 (32)	5.96 (24)	1.67 (2)	
Comorbidities					
Hypertension	73.0 (748)	73.6 (359)	71.1 (295)	77.7 (94)	.33
Diabetes	15.9 (150)	17.0 (76)	16.1 (62)	10.8 (12)	.27
Dyslipidemia	38.1 (392)	38.1 (189)	37.7 (155)	39.3 (48)	.95
History of stroke or TIA	7.48 (77)	8.27 (41)	7.04 (29)	5.74 (7)	.58
History of depression	23.4 (241)	21.8 (108)	23.8 (98)	28.7 (35)	.27
Global cognitive assessment					
MMSE (/30), M (SD)	24.4 (3.8)	22.2 (3.8)	26.1 (2.5) [†]	27.4 (2.1) [†]	<.0001
ADL score (/6), M (SD)	5.81 (0.54)	5.72 (0.67)	5.90 (0.38)	5.85 (0.31)	<.0001
IADL score (/14), M (SD)	11.8 (2.8)	10.8 (3.3)	12.7 (2.0)*	13.1 (1.6)*	<.0001
GDS (/30), M (SD)	7.68 (5.06)	7.52 (5.03)	7.70 (5.04)	8.33 (5.31)	.34
Hippocampal volume (R + L) (cm ³), M (SD)	4.26 (1.24)	3.93 (1.26)	4.44 (1.17) [†]	5.00 (0.87) [†]	<.0001

Abbreviations: ADL, activities of daily living; aMCI, amnesic mild cognitive impairment; ANOVA, analysis of variance; BALTAZAR, Biomarker of AmyLoid pepTide and AlZheimer's diseAse Risk; BMI, body mass index; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; M (SD), mean (standard deviation); MMSE, Mini-Mental State Examination; naMCI, nonamnesic mild cognitive impairment; R + L, right + left; TIA, transient ischemic attack.

NOTE. Comparison between aMCI and naMCI: **P* < .05 and [†]*P* < .001.

[‡]Comparison between the three groups, with ANOVA or χ^2 .

Correlations between plasma amyloid biomarkers and the other parameters are shown in Table 3, Fig. 2, and Supplementary Table 2.

Plasma A β_{1-42} correlated with age in AD, all MCI and aMCI (*P* < .001 for all), and with MMSE in the AD group (*P* = .04). In all MCI, plasma A β_{1-42} was associated with the presence of APOE $\epsilon 4$ allele (*P* = .003) and CSF A β_{42} , Tau, p-Tau and p-Tau/A β_{42} ratio (*P* = .02, *P* = .01, *P* = .02 and *P* = .002 respectively) (Fig. 2 and Supplementary Table 2). In aMCI groups, plasma A β_{1-42} was associated with APOE $\epsilon 4$ allele (*P* = .03) and with Tau, p-Tau and p-Tau/A β_{42} ratio (*P* = .02, *P* = .03, *P* = .004, respectively; Fig. 2 and Supplementary Table 2). In AD participants, plasma A β_{1-42} only correlated with CSF A β_{42} (*P* = .01).

Plasma A β_{1-40} significantly correlated with age in AD, all MCI and aMCI (*P* < .01 for all). Plasma A β_{1-40} marginally correlated with Tau, p-Tau and p-Tau/A β_{42} ratio in AD and naMCI (Supplementary Table 2).

Significant relationships between CSF and plasma biomarkers remained significant when the models were adjusted for age, sex, and presence of APOE $\epsilon 4$ allele (see Supplementary Table 2).

No correlation between hippocampal volume and plasma A β_{1-42} was found, however a correlation was observed between the plasma A β_{1-40} level and the hippocampal volume in AD (*P* = .05).

When MCI were defined based on amyloid and neuronal biomarkers according to National Institute on Aging criteria, CSF A β_{1-42} , Tau and p-Tau were all different between MCI core clinical, MCI low-likelihood, MCI intermediate-likelihood and MCI high-likelihood (*P* < .0001 for all). For plasma biomarkers the overall differences between the groups of A β_{1-40} and A β_{1-42} were not significant (A β_{1-40} : 267 [63], 281 [60], 271 [70] and 272 [69], *P* = .51 and A β_{1-42} : 39.3 [11.6], 38.9 [12.5], 39.0 [12.4] and 35.6 [10.1], *P* = .14 respectively). However, the differences of A β_{1-42} between MCI low-likelihood and MCI high-likelihood was significant (*P* = .03).

4. Discussion

In our study, plasma A β_{1-42} and A β_{1-40} levels were lower in AD than in aMCI than in naMCI participants. Interestingly, plasma A β_{1-42} correlated with the three CSF

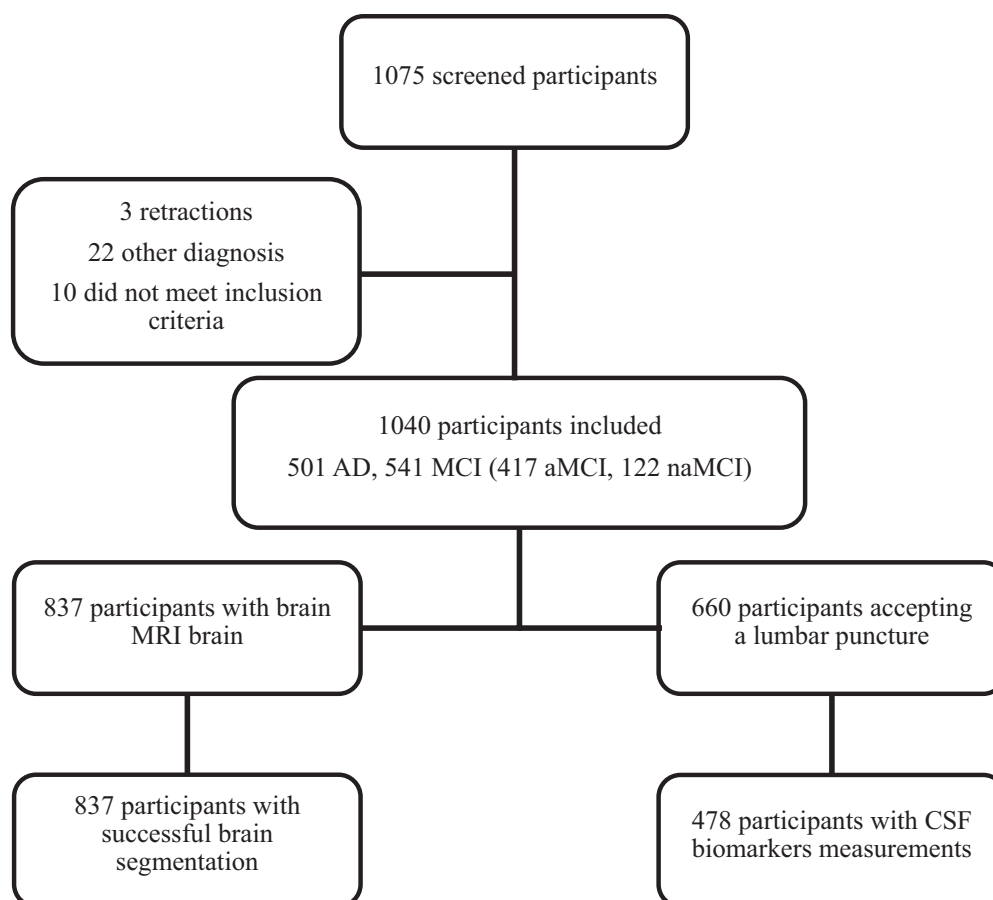


Fig. 1. Flow chart of the study. Abbreviations: AD, Alzheimer's disease; aMCI, amnesic mild cognitive impairment; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; naMCI, nonamnesic mild cognitive impairment.

biomarkers in all MCI but only with CSF $A\beta_{42}$ in AD. A correlation was also found between plasma $A\beta_{1-42}$ and MMSE in AD. In aMCI participants, plasma $A\beta_{1-42}$ correlated with CSF tau and p-Tau. Taking into account preanalytical and analytical potential confounding factors, our findings suggested the relevance of plasma amyloid biomarkers in the Alzheimer's process. We confirmed also previous results [17,29]. Our data are in accordance with the potential

different kinetic of plasma $A\beta$ levels in AD, in MCI, and in controls, with higher baseline levels in naMCI than aMCI and a decrease in MCI at-risk for AD [30]. Comparison of studies assessing plasma $A\beta$ peptides remains difficult as different technologies have been used to measure plasma $A\beta$ (ELISA, Luminex, MSD, or Simoa technology). However, the standardization is still ongoing with the development of certified reference material [31].

Table 2

Plasma and CSF biomarkers concentrations at baseline according to the cognitive status

Biomarkers, M (SD)	AD	Amnesic MCI	Nonamnesic MCI	<i>P</i> *
Plasma biomarkers	N = 426	N = 373	N = 113	
$A\beta_{1-42}$ (pg/mL)	36.9 (11.7)	38.2 (11.9)	39.7 (10.5)	.01
$A\beta_{1-40}$ (pg/mL)	263 (80)	269 (68)	272 (52)	.04
$A\beta_{1-42}/A\beta_{1-40}$ ratio	0.160 (0.120)	0.154 (0.105)	0.148 (0.039)	.21
CSF biomarkers	N = 213	N = 210	N = 55	
$A\beta_{42}$ (pg/mL)	729 (292)	864 (390)	1004 (351)	<.0001
Tau (pg/mL)	583 (249)	470 (221)	326 (136)	<.0001
p-Tau (pg/mL)	81.6 (36.5)	70.5 (31.1)	54.2 (17.1)	<.0001
p-Tau/ $A\beta_{42}$ ratio	0.133 (0.088)	0.108 (0.085)	0.0634 (0.0355)	<.0001

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; M (SD), mean (standard deviation); MCI, mild cognitive impairment; p-Tau, phosphorylated tau.

*Comparison between the three groups with linear regression adjusted for age, sex, educational level, and the presence of the *APOE* $\epsilon 4$ allele.

Table 3

Relationship between plasma biomarkers and age, MMSE score, the presence of the *APOE* $\epsilon 4$ allele, and the hippocampal volume in the whole sample and among AD, MCI, aMCI, and naMCI groups

Characteristics	Plasma $A\beta_{1-40}$ (pg/mL)		Plasma $A\beta_{1-42}$ (pg/mL)	
	Mean (SD) or ρ	<i>P</i>	Mean (SD) or ρ	<i>P</i>
Whole sample, N = 912				
Age	0.199	<.0001	0.186	<.0001
MMSE	0.0359	.29	0.099	.003
<i>APOE</i> $\epsilon 4$ allele				
0	268 (73)		38.9 (12.1)	
1	264 (66)	.03	36.1 (10.8)	.0004
2	242 (71)		34.7 (9.1)	
Hippocampal volume (R + L)	-0.0564	.12	0.0421	.25
AD, N = 426				
Age	0.236	<.0001	0.207	<.0001
MMSE	0.0176	.72	0.102	.04
<i>APOE</i> $\epsilon 4$ allele				
0	259 (81)		37.5 (12.5)	
1	261 (71)	.31	35.4 (10.4)	.16
2	238 (85)		35.0 (9.3)	
Hippocampal volume (R + L)	-0.106	.05	0.0195	.71
All MCI, N = 486				
Age	0.141	.002	0.161	.0004
MMSE	0.0138	.76	0.0467	.31
<i>APOE</i> $\epsilon 4$ allele				
0	274 (68)		39.8 (11.7)	
1	267 (60)	.11	36.7 (11.1)	.003
2	247 (50)		34.2 (9.0)	
Hippocampal volume (R + L)	-0.0298	.56	0.0203	.69
Amnesic MCI, N = 373				
Age	0.137	.008	0.158	.002
MMSE	-0.00135	.98	0.0141	.79
<i>APOE</i> $\epsilon 4$ allele				
0	273 (73)		39.5 (12.2)	
1	268 (63)	.19	36.6 (11.4)	.03
2	245 (51)		34.5 (9.3)	
Hippocampal volume (R + L)	-0.0396	.49	-0.0137	.81
Nonamnesic MCI, N = 113				
Age	0.16	.09	0.165	.08
MMSE	0.0737	.45	0.151	.12
<i>APOE</i> $\epsilon 4$ allele				
0	276 (54)		40.7 (10.6)	
1	261 (44)	.43	37.3 (9.8)	.15
2	266 (19)		30.0 (1.4)	
Hippocampal volume (R + L)	0.00881	.94	0.166	.13

Abbreviations: ρ , Pearson correlation coefficient; AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; R + L, right + left; SD, standard deviation.

Plasma $A\beta_{1-42}$ and $A\beta_{1-40}$ levels were progressively lower from naMCI to aMCI and to AD participants. This result is in accordance with recent study that also observed both plasma $A\beta_{1-42}$ and $A\beta_{1-40}$ decreases in AD [29] but not in others [32-34]. The decrease of plasma amyloid level during the Alzheimer's process could be explained by $A\beta$ clearance decrease from the brain (CSF) to the peripheral fluid (blood) because of alteration of blood-brain barrier permeability, glymphatic system, or vascular or microglial activation troubles [35,36]. Interestingly, the proportion of $A\beta_{1-42}$ reduction between the clinical groups was similar in the two fluids (3.7% and 7.3% in plasma and 14% and 28% in CSF for aMCI vs. naMCI and AD vs. naMCI, respectively). This

suggests that plasma $A\beta_{42}$ variations reflect CSF $A\beta_{42}$ variations. It remains difficult to argue for or against the peripheral sink theory hypothesizing that the reduction of $A\beta$ peptides in the blood is a mechanism to diminish $A\beta$ levels and plaque load in the brain. Our results also fit the second part of the Song et al. model [7] in which plasma $A\beta_{42}$ decreases during the course of the disease. For the first part, Song et al. hypothesize that plasma $A\beta_{42}$ levels are higher in MCI subjects when compared to controls. In the present study, no control group was included but the longitudinal follow-up of the BALTAZAR study will enable the comparison of repeated measures of plasma $A\beta$ over time and the analysis of their changes according to Alzheimer's continuum.

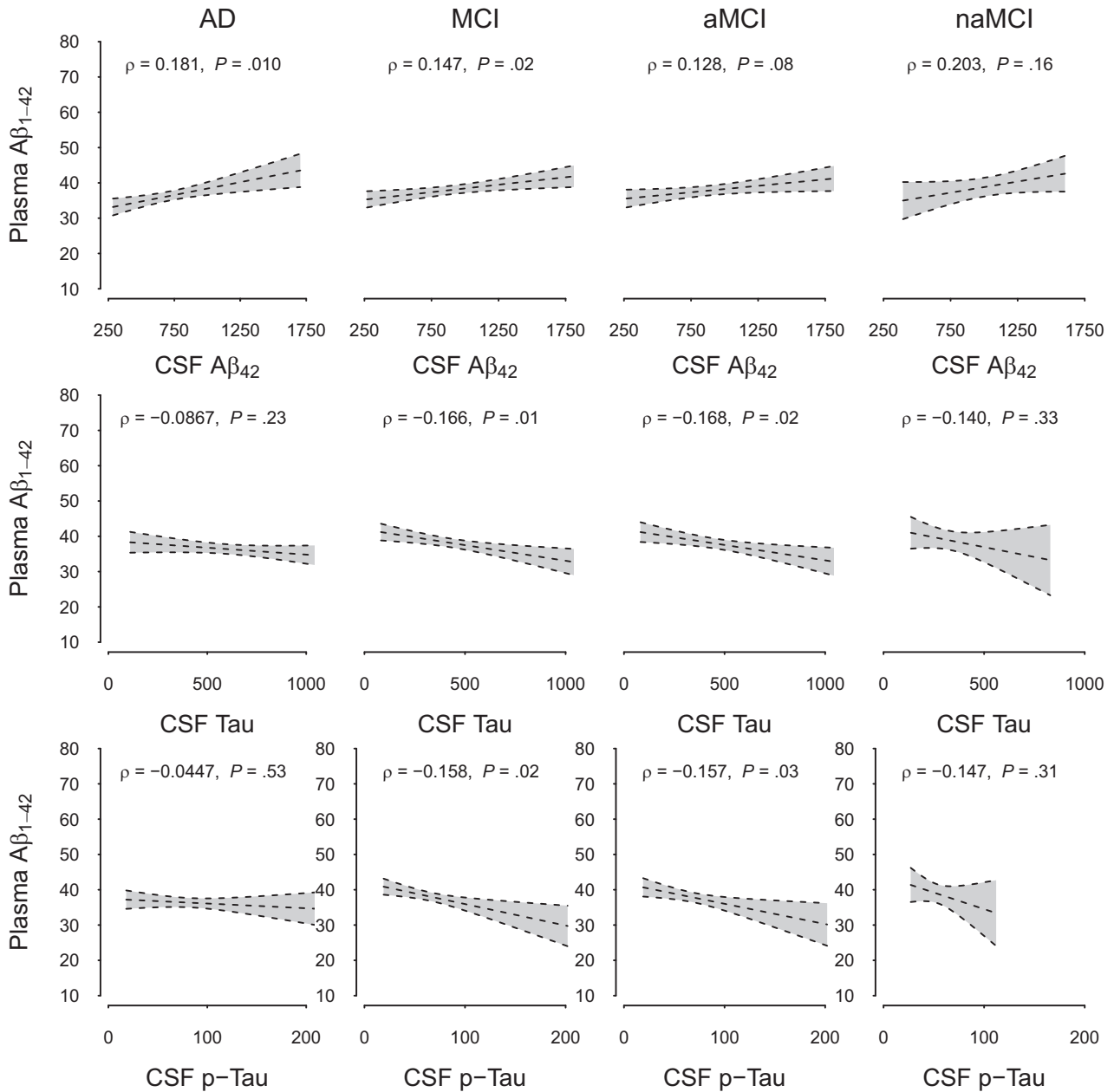


Fig. 2. Correlations between plasma Aβ₁₋₄₂ and CSF Aβ₄₂, tau, and p-Tau in the AD, MCI, aMCI, and naMCI groups. Abbreviations: Aβ, amyloid β; aMCI, amnesic mild cognitive impairment; AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; naMCI, nonamnesic mild cognitive impairment; p-Tau, phosphorylated tau.

Plasma Aβ₁₋₄₂ correlated with CSF Aβ₄₂ biomarkers in MCI and AD patients. This correlation has been previously described with amyloid brain lesions in postmortem [37,38] and studies using PET imaging with the Pittsburgh Compound-B. In the BioFINDER study including 719 elderly subjects with subjective cognitive decline, MCI, AD, and healthy cognition, the Aβ₄₂ level is lower in AD compared to control, subjective cognitive decline, and MCI groups and that low plasma Aβ₄₂ and Aβ₄₂/Aβ₄₀ ratio are associated with brain amyloid deposits measured by amyloid-PET [29].

Interestingly, we found that plasma Aβ₁₋₄₂ negatively correlated with CSF tau and p-Tau only in MCI participants. Plasma Aβ₄₂ levels may be correlated with some specific release of tau forms in the early stages of AD process. CSF tau forms are numerous (splice variants, phosphorylated/glycosylated forms, truncated and membrane associated forms, etc.) [39,40]. The relationship between plasma Aβ₁₋₄₂ and tau could be of two types: either (1) direct, Aβ₄₂ has been shown to induce tau phosphorylation [41] or (2) indirect, through common mechanisms influencing amyloid and tau metabolism,

that is, lipid and glucose metabolism or *APOE* [42]. In this way, recent findings show that $A\beta_{42}$ influences neuronal death that increases release of tau aggregation competent forms [43]. Another hypothesis could be that the dynamic of plasma $A\beta_{42}$, CSF p-Tau, and tau levels differs at MCI and AD stages. Level of tau and p-Tau increases during the MCI stage of the disease and reaches a plateau at the demented stage [2]. At the latest stage, the remaining neurons are probably not numerous enough to maintain the increase of CSF tau and p-Tau, and the $A\beta$ in the plasma and tau processes are thus dissociated. According to amyloid cascade, a certain amount of soluble $A\beta_{42}$ could be needed in periphery to affect brain tau metabolism, and the alteration of the blood-brain barrier permeability within the process could influence the toxicity of peripheral amyloid products. Conversely tau aggregation seems influenced $A\beta$ metabolism and elimination from brain [44].

Despite correlations between plasma $A\beta_{42}$ and tau markers, we only found a trend between high level of plasma $A\beta_{40}$ and a reduction of the hippocampal volume, which is consistent with the findings of the 3C study in which higher plasma $A\beta_{40}$ is correlated to a higher atrophy score in dementia-free older adults [45] but not with the results of the Sydney Memory and Ageing Study [46].

The strength of our study lies in the large number of well-characterized participants with harmonized and standardized cognitive tests. We optimized the data through reclassified participants based on CSF or MRI biomarkers to determine amyloid and neuronal injury process. All the biochemical analyses were centralized in a single laboratory, eliminating intercenter variability. To limit confounding effects, the same preanalytical protocol was followed throughout the study, with shipment to all centers of the same collection tubes. The same lot was used for measurement of plasma amyloid levels at inclusion. We used the commercially available Luminex technology that has good analytical performances and clinical sensitivity and is already used in routine [47]. In addition, the brain MRI was analyzed in one dedicated expert center.

The present study has some limitations. No amyloid-PET imaging or neuropathological confirmation was available. The analysis is cross-sectional, as the clinical, neuropsychological, and imaging follow-up is still ongoing. We did not adjust the analysis for MCI duration although it may have affected both plasma and CSF biomarkers levels because duration of MCI disease is very difficult to assess and were thus not recorded. Inclusion of healthy controls would have provided a better evaluation of plasma $A\beta$ as a marker of MCI; however, we did not include healthy controls because it is ethically difficult to propose a lumbar puncture to subjects without cognitive complaint. The prospective design of the BALTAZAR study will enable the analysis of predictive value of plasma $A\beta$ for conversion from MCI to AD and severe worsening of AD.

To conclude, our findings open new insights to better understand the link between peripheral and central biomarkers within the Alzheimer's process at an early stage. Plasma $A\beta$ was associated with cognitive status and CSF biomarkers. Plasma $A\beta_{1-42}$ and $A\beta_{1-40}$ levels were lower in AD than in aMCI than in nMCI participants. This needs to be further investigated in a longitudinal follow-up to assess the potential prognosis relevance of plasma amyloid biomarkers. Regarding the correlation between plasma $A\beta_{42}$ and CSF tau biomarkers in MCI, further studies including PET-tau biomarkers and new innovative techniques to detect specific tau forms will be interesting.

Acknowledgments

The BALTAZAR study is supported by a grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique [PHRC 2009/01-04 and PHRC-13-0404]) and by the Fondation Plan Alzheimer.

Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jalz.2018.01.004>.

RESEARCH IN CONTEXT

1. Systematic review: Peripheral biomarkers are needed for diagnosis and management of Alzheimer's disease (AD) patients because the cerebrospinal fluid (CSF) biomarker and amyloid positron emission tomography are not usable as screening tools. Plasma amyloid β ($A\beta$) seems the most promising biomarker, although previous studies found controversial results. We report the associations of plasma $A\beta$ and cognitive status and CSF biomarkers at baseline in a multicenter prospective study (1040 participants: 417 amnesic mild cognitive impairment [MCI], 122 nonamnesic MCI, and 501 AD).
2. Interpretation: Plasma $A\beta$ decreased from nonamnesic MCI to amnesic MCI and to AD. Globally, plasma $A\beta$ correlated with age, Mini-Mental State Examination, *APOE* $\epsilon 4$ and correlated with all CSF biomarkers in MCI but only with CSF $A\beta$ in AD. Peripheral $A\beta$ and central $A\beta$ were correlated at early stage, suggesting the interest of plasma amyloid biomarkers for diagnosis purpose.
3. Future direction: The follow-up is ongoing and will enable the analysis of predictive values of plasma $A\beta$ for conversion from MCI to AD and rapid worsening of AD.

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