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Markers of neuroinflammation associated with Alzheimer's disease pathology in older adults

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Keywords: Alzheimer's disease, mild cognitive impairment, neuroinflammation, biomarkers, amyloid, tau

Abstract

BACKGROUND:

In vitro and animal studies have linked neuroinflammation to Alzheimer's disease (AD) pathology. Studies on markers of inflammation in subjects with mild cognitive impairment or AD dementia provided inconsistent results. We hypothesized that distinct blood and cerebrospinal fluid (CSF) inflammatory markers are associated with biomarkers of amyloid and tau pathology in older adults without cognitive impairment or with beginning cognitive decline.

OBJECTIVE:

To identify blood-based and CSF neuroinflammation marker signatures associated with AD pathology (i.e. an AD CSF biomarker profile) and to investigate associations of inflammation markers with CSF biomarkers of amyloid, tau pathology, and neuronal injury.

DESIGN/METHODS:

Cross-sectional analysis was performed on data from 120 older community-dwelling adults with normal cognition (n = 48) or with cognitive impairment (n = 72). CSF Aβ1-42, tau and p-tau181, and a panel of 37 neuroinflammatory markers in both CSF and serum were quantified. Least absolute shrinkage and selection operator (LASSO) regression was applied to determine a reference model that best predicts an AD CSF biomarker profile defined *a priori* as p-tau181/Aβ1-42 ratio >0.0779. It was then compared to a second model that included the inflammatory markers from either serum or CSF. In addition, the correlations between inflammatory markers and CSF Aβ1-42, tau and p-tau181 levels were assessed.

RESULTS:

Forty-two subjects met criteria for having an AD CSF biomarker profile. The best predictive models included 8 serum or 3 CSF neuroinflammatory markers related to cytokine mediated inflammation, vascular injury, and angiogenesis. Both models improved the accuracy to

predict an AD biomarker profile when compared to the reference model. In analyses separately performed in the subgroup of participants with cognitive impairment, adding the serum or the CSF neuroinflammation markers also improved the accuracy of the diagnosis of AD pathology.

None of the inflammatory markers correlated with the CSF Aβ1-42 levels. Six CSF markers (IL-15, MCP-1, VEGFR-1, sICAM1, sVCAM-1, and VEGF-D) correlated with the CSF tau and p-tau181 levels, and these associations remained significant after controlling for age, sex, cognitive impairment, and APOEε4 status.

CONCLUSIONS:

The identified serum and CSF neuroinflammation biomarker signatures improve the accuracy of classification for AD pathology in older adults. Our results suggest that inflammation, vascular injury, and angiogenesis as reflected by CSF markers are closely related to cerebral tau pathology.

1. Introduction

Neuroinflammation has long been known as an accompanying pathology of Alzheimer's disease (AD). It is now well-established that localized low-level inflammation occurs early in the AD brain. In vitro and animal studies demonstrated the activation of different inflammatory pathways in association with amyloid pathology and tau-related neurodegeneration during the course of the disease. (Calsolaro and Edison, 2016; Heppner et al., 2015) In humans, genetic studies identified associations between polymorphisms in genes related to the immune system and the risk of AD (Calsolaro and Edison, 2016; Heneka et al., 2015), while histopathological studies suggested that glial activation is an important mediator of neurotoxicity and altered cognition in the presence of amyloid and tau pathology (Perez-Nievas et al., 2013). The inflammatory process driven by activated and proliferating glial cells, but also astrocytes, other myeloid cells, epithelium and other reactive elements leads to increased production and release of proinflammatory cytokines, chemokines and other mediators of inflammation. These factors may exacerbate amyloid production and toxicity, and contribute to tau hyperphosphorylation and neuronal injury. Vascular injury and endothelial dysfunction in relation to inflammation are also common in AD. They lead to the accumulation of several vasculotoxic and neurotoxic molecules within brain parenchyma, thus likely contributing to a noxious milieu finally promoting neuronal dysfunction and death (Grammas, 2011; Zlokovic, 2011). Several studies in subjects with mid cognitive impairment (MCI) and AD dementia revealed increased inflammatory activity in both the CNS and the circulating blood. However, reports on cytokines and other markers of inflammation in MCI or AD were controversial or inconsistent so far (Brosseron et al., 2014; Delaby et al., 2015; Hesse et al., 2016).

The development of AD pathology starts many years before the onset of the first clinical signs. Older subjects with normal cognition may already have cerebral AD pathology and may be

seen as being at the preclinical stage of the disease (Sperling et al., 2011). On the other hand, subjects with cognitive deficits may have cognitive impairment not primarily or only in part related to AD pathology. New research criteria consider AD as a biological continuum across the clinical spectrum from asymptomatic stage to advanced dementia, and emphasize the utility of biomarkers of AD pathology for an accurate diagnosis, in particular at the preclinical and prodromal disease stages (Albert et al., 2011; Dubois et al., 2014; Sperling et al., 2011).

In this study, we aimed at identifying blood and cerebrospinal fluid (CSF) inflammation marker profiles related to the presence of cerebral AD pathology in older adults without cognitive impairment and with beginning cognitive decline. Furthermore, we hypothesized that blood and CSF inflammatory markers of cytokine mediated inflammation, vascular injury, and angiogenesis are associated with CSF biomarkers of amyloid and tau pathology.

2. Material and Methods

2.1 Subjects

One hundred and twenty community dwelling participants were included in this study, of whom 48 were cognitively healthy volunteers and 72 had mild cognitive impairment (MCI, N=63) or mild dementia of AD type (N=9). The participants with cognitive impairment were recruited among patients attending the Memory Clinic of the Old-Age Psychiatry service and the Leenaards Memory Centre of the Lausanne University Hospital. They had no major psychiatric or neurological disorders, nor substance abuse or severe or unstable physical illness that may contribute to cognitive impairment, and met the diagnostic criteria for MCI (Winblad et al., 2004) or mild dementia. The control subjects were recruited through journal announcements or word of mouth and had no history, symptoms, or signs of relevant psychiatric or neurologic disease and no cognitive impairment. All participants had a comprehensive medical, psychiatric, neuropsychological and psychosocial evaluation, as well

as brain MRI or CT scans, and venous and lumbar punctures. The MRI and CT scans were used in order to exclude cerebral pathologies possibly interfering with the cognitive performance.

The diagnosis of MCI or mild dementia of AD type was based on neuropsychological and clinical evaluation and was made by a consensus conference of neuropsychologists, psychiatrists, and/or neurologists prior to inclusion into the study. MCI was diagnosed according to consensus recommendations (Winblad et al., 2004). The participants in this group had memory impairment (<–1.5 standard deviation (SD) below the mean, adjusted for gender, age and education in the verbal memory task of Buschke Double Memory Test (Buschke et al., 1997a)) and/or impairment in another cognitive domain, and a Clinical Dementia Rating (CDR) (Morris, 1993) score of 0.5. The diagnosis of mild AD dementia was based on the clinical diagnostic criteria for probable dementia due to AD according to recommendations from the National Institute on Aging and Alzheimer's Association (McKhann et al., 2011) and DSM-IV criteria for dementia of the Alzheimer type (American-Psychiatric-Association, 1994). Participants in this group had a CDR score of 1. The subjects with MCI and mild dementia were considered as one group with CDR>0). The participants without cognitive impairment had no history or evidence of cognitive deficits, and their CDR score was 0.

Neuropsychological tests were used to assess cognitive performance in the domains of memory -Buschke Double Memory Test (Buschke et al., 1997b), language -a verbal fluency task (categorical and literal fluency in 2 min)executive functions: a speed of processing and cognitive flexibility task - the Trail Making Test A and B (Reitan, 1958), an inhibition task - the Stroop test (Bayard et al., 2009), and visuo-constructive functions (CERAD copy image test). The Mini Mental State Examination (Folstein et al., 1975) was used to assess participants' global cognitive performance. Depression and anxiety were assessed using the

Hospital Anxiety and Depression scale (HAD) (Zigmond and Snaith, 1983). The psychosocial and functional assessment included the ADL (Katz, 1997) and instrumental ADL (Lawton and Brody, 1970), the NPIQ (Cummings et al., 1994) and the IQCODE (Jorm and Jacomb, 1989) questionnaires and were completed by the family members of the participants. All tests and scales are validated and widely used in the field.

The study was approved by the local ethics committee and written informed consent to participate in the study was obtained from all participants.

2.2 Cerebrospinal fluid AD biomarkers and APOE genotyping

Venous and lumbar punctures were performed between 8:30 and 9:30 am after overnight fasting at the recruiting memory centre. CSF was collected by lumbar puncture, using a standardized technique with a 22G "atraumatical" spinal needle while the patient was sitting or lying (Popp et al., 2007). Ten to twelve ml of CSF were obtained using polypropylene tubes. Routine cell count and protein quantification were performed. Remaining CSF and blood was frozen in aliquots no later than 1 h after collection and stored at -80 °C without thawing until assay. CSF Aβ1-42, total-tau (tau), and tau phosphorylated at threonine 181 (ptau181) concentrations were measured using commercially available ELISA kits (Fujirebio, Gent, Belgium). The APOE genotype was determined and considered in all main analytical steps to evaluate possible interactions and effects on the addressed relationships (Jansen et al., 2015; Popp et al., 2010). DNA was extracted from whole blood using the QIAsymphony DSP DNA Kit (Qiagen, Hombrechtikon, Switzerland). The SNV rs429358 and rs7412 were genotyped using the Taqman assays C___3084793_20 and C____904973_10 respectively (Thermo Fischer Scientific, Waltham, MA, USA).

A pathological CSF AD biomarker profile was defined as a p-tau181/Aβ1-42 ratio >0.0779, based on clinical study site data (Tautvydaite et al., 2016) and in line with previous

publications (Duits et al., 2014). Briefly, the cutoff was determined from 48 healthy volunteers with normal cognition and 72 memory clinic patients with MCI or mild dementia of AD type as the value that optimized the Youden index of the Received Operating Characteristic (ROC) curve of prediction of CDR categories (CDR = 0 vs. CDR > 0; AUC=0.789, accuracy: 0.733). This cutoff was further confirmed to be a highly significant predictor of cognitive decline (i.e. change in global cognition as measured by MMSE at a follow-up visit 18 months after inclusion) in models adjusted for multiple possible confounders (Beta=-0.436; $p<0.00001$; unpublished data)

2.3 Neuroinflammatory markers

Paired serum and CSF samples were measured using the V-Plex Neuroinflammation Panel 1 (Meso Scale Discovery (MSD), Rockville, MD, USA). The Panel consisting of 38 analytes was run according to product protocol. The 96-well plates pre-coated with capture antibodies were blocked with 5% MSD Blocker A Solution. Calibrator dilutions were prepared and samples were diluted as recommended for each kit with MSD Diluents. Samples and calibrators were then added to the plates and incubated at room temperature with shaking for 2 h. Plates were washed three times with a home-prepared solution of 10 × phosphate-buffered saline (PBS), pH 7.4 (Corning, VA, USA)-Tween 20 (Fisher Scientific, PA, USA). Detection antibodies were mixed with MSD Diluents as indicated in the protocols of each kit and incubated at room temperature with shaking for 1-2 h. Plates were washed three times with the PBS-Tween 20 solution. MSD Read buffer was added and plates were read on an MSD instrument (SECTOR Imager 6000 reader). Data were generated and interpolated using MSD Discovery Workbench software.

2.4 Pre-analytical quality controls and filtering

Biomarkers with more than 5% missing data or below-level-of-quantification limits were filtered out, ending up with a selection of 37 analytes: IFNγ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, TNFα, IL-1α, IL-5, IL-7, IL-12/23p40, IL-15, IL-16, IL-17A, TNFβ, VEGF-A, Eotaxin, MIP-1β, Eotaxin-3, TARC, IP-10, MIP-1α, MCP-1, MDC, MCP-4, VEGF-C, VEGF-D, Tie-2, sFLT-1 (VEGFR-1), pIGF-1R, bFGF (FGF-2), SAA1, CRP, sVCAM-1, and sICAM-1. IL-12p70 was not included. Remaining missing data (5% or less per biomarker) were imputed by randomly drawing a measure between in the observed range of biomarker values. Biomarker data was $\log_{10}$-transformed to approach a Gaussian distribution, and standardized prior to statistical analyses. One low quality CSF sample and two serum samples could not be analyzed. Therefore serum and CSF neuroinflammatory biomarker data were available for 118 and 119 subjects, respectively.

2.5 Statistical analyses

Least absolute shrinkage and selection operator (LASSO) logistic regression (Tibshirani, 1996) was used to select relevant biomarker features and build a predictive model of AD CSF biomarker profiles. All biomarker variables were included in the model, together with the variables used in a reference model (age, sex, years of education, and presence of APOE ε4 allele) that was tested independently. CSF and serum biomarkers were tested separately. A 10-fold cross-validation process was performed for each LASSO analysis using the *glmnet* package (Friedman et al., 2010), which permitted to estimate the confidence interval of the misclassification error for each value of the regularization parameter. The LASSO analysis was repeated 100 times. The model that minimized the cross-validated misclassification error across the 100 runs was selected. Its performance was assessed by ROC AUC estimation (using a bootstrap approach with 1000 iterations) and compared with the reference model AUC and accuracy (using a McNemar test).

Two-sided correlation analyses between neuroinflammatory biomarkers and AD CSF markers (Aβ1-42, tau and p-tau181) were performed with the Pearson's statistics and resulting p-values were adjusted for multiple-testing using Bonferroni correction.

Neuroinflammatory markers significantly ($p < 0.05$) correlated with an AD CSF marker (Aβ42, tau or p-tau181) were further studied in a linear regression model with the AD CSF marker as the dependent variable and the following list of explanatory covariates: each neuroinflammatory marker, age (in years), sex (categorical: male vs. female), APOE ε4 status (categorical, presence vs. absence of at least one ε4 allele), CDR (categorical: >0, i.e. subjects with MCI and mild dementia considered as one group vs. 0), and albumin quotient (only for serum neuroinflammatory biomarkers). Values of the regression terms were reported and their differences from 0 were assessed with *t*-tests. Interaction terms between the neuroinflammatory markers and separately age, sex, CDR, and APOE ε4 status were further tested in a type II Analysis of Variance (ANOVA) with a F-test.

3. Results

Demographics and clinical characteristics of the patient cohort are detailed in Table 1. Participants with cognitive impairment (CDR > 0) were significantly older than subjects with normal cognition (CDR = 0).

Table 1 – Demographics and clinical characteristics

	CDR = 0 (n = 48)	CDR > 0 (n = 72)
Age (years), mean (SD)	66.0 (7.4)	73.3 (6.9)*
Gender, No. (%) of Males	17 (35.42%)	26 (36.11%)

Education years, mean (SD)	13.2 (2.3)	11.8 (2.7)*
MMSE scale, mean (SD)	28.5 (1.4)	25.9 (3.5)*
APOEε4 carriers, No. (%)	11 (22.92%)	26 (36.11%)*
CSF Aβ 1-42 (pg/mL), mean (SD)	957.4 (194.0)	774.0 (281.5)*
CSF tau (pg/mL) , mean (SD)	221.5 (82.9)	471.1 (316.6)*
CSF p-tau181 (pg/mL), mean (SD)	45.9 (13.3)	72.7 (40.9)*
p-tau/Aβ 1-42, mean (SD)	0.049 (0.015)	0.114 (0.097)*
AD CSF biomarker profile, No. (%)	1 (2.08%)	41 (56.94%)*
Albumin ratio, mean (SD)	5.3 (1.9)	6.6 (2.5)*

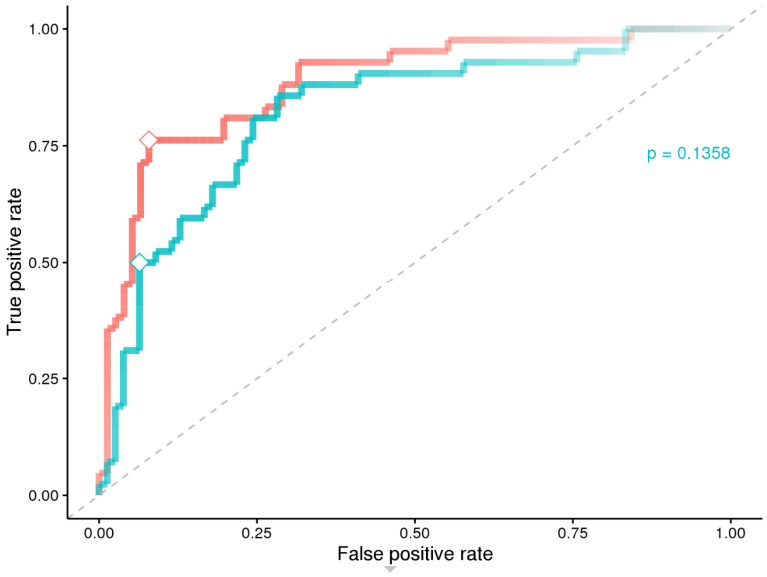
*statistically different ($p \leq 0.05$) from CDR 0, using t-tests for continuous variables and binomial proportion tests for categorical variables.

APOEε4 = Apolipoprotein E ε4 allele; MMSE = Mini Mental State Examination

The reference LASSO classifier generated an accuracy of 78.3% and a ROC AUC of 0.83 [0.74 - 0.90]. The LASSO analyses performed by adding the inflammatory markers, separately CSF and serum, outperformed the reference classifier significantly in terms of accuracy but not in terms of AUC. The model including the serum inflammatory markers generated an accuracy of 86.4% ($p = 0.01$) and ROC AUC 0.89 [0.81 – 0.95] ($p = 0.14$, Figure 1a). Eight serum biomarkers were selected in this predictive model: bFGF, CRP, IL-16, sFLT-1, sICAM-1, Tie-2, VEGF-C, and VEGF-D (Figure 2a). The CSF neuroinflammatory model had an accuracy of 85.7% ($p = 0.02$ as compared with the reference model) and ROC AUC 0.90 [0.83 – 0.95] ($p = 0.08$, Figure 1b). Three biomarkers were selected in this predictive model: IL-15, MCP-1, and sFLT-1 (VEGFR-1) (Figure 2b). When performed in the 72 subjects with cognitive impairment only (CDR > 0), the model including the serum

inflammatory markers had an accuracy of 91.7% (p = 0.02) as compared with the reference model in this sub-population (accuracy of 77.8%) and ROC AUC 0.96 [0.89 – 0.99] (p < 0.01, Supplementary Figure a). The corresponding CSF neuroinflammatory model had an accuracy of 90.3% (p = 0.07) and AUC 0.93 [0.85 - 0.97] (vs. reference model ROC AUC 0.83 [0.73 – 0.91], p = 0.04 (Supplementary Figure b).

(a)



(b)

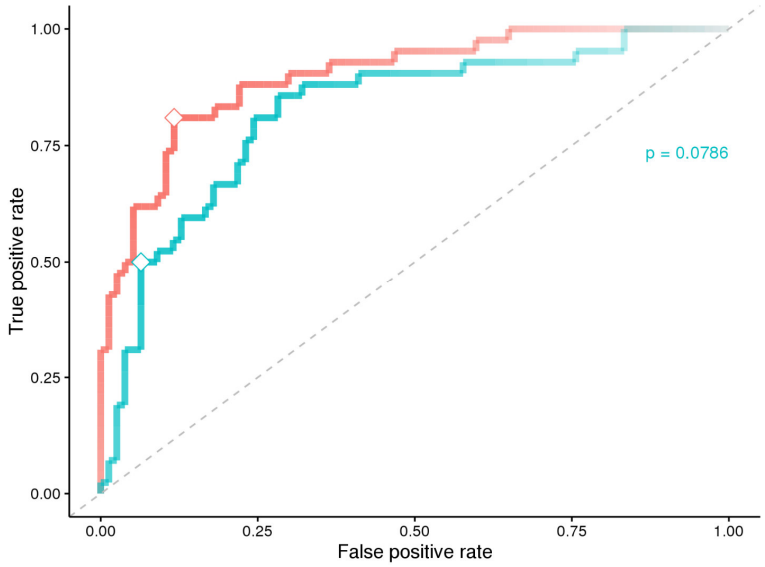
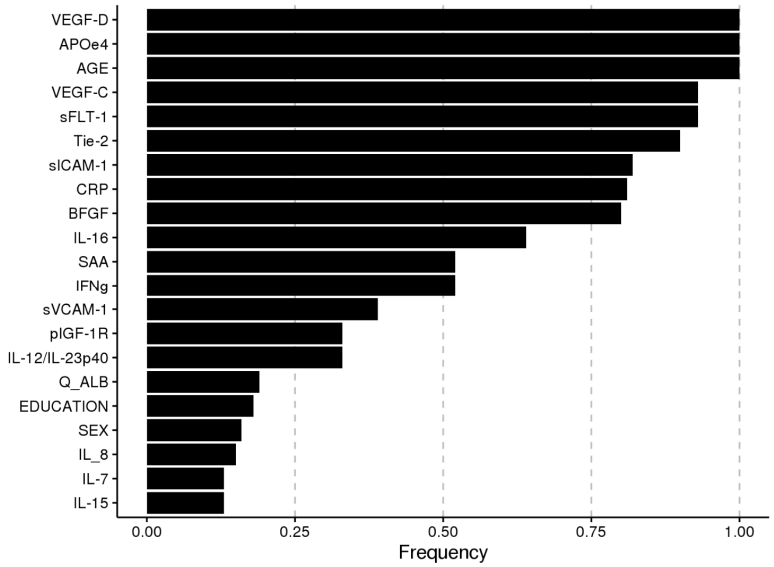


Figure 1 – ROC curves of the serum *(a)* and CSF *(b)* models predictive of biomarker CSF profile.

The ROC curves of the LASSO models including neuroinflammatory biomarkers (in red) are compared with the ROC curves of the reference LASSO models (in blue). The opacity of the curves is proportional to the accuracy of the models. The diamonds indicate the selected most accurate models. The p-values on the graphs indicate the significance of the differences of AUC. The biomarkers models had a ROC AUC of 0.89 [0.81 - 0.95] in serum and of 0.90 [0.83 - 0.95] in CSF.

(a)



(b)

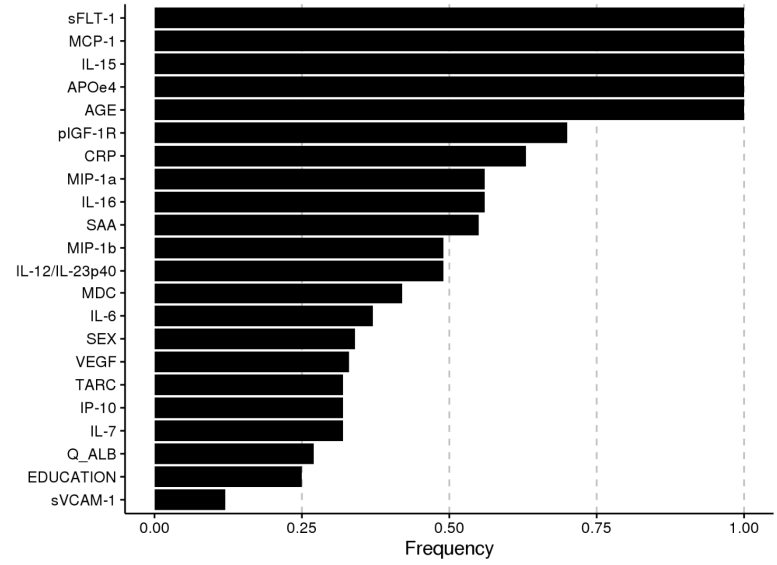


Figure 2. Frequencies of selected markers in all LASSO models.

The LASSO analyses were repeated 100 times, each time selecting possibly different biomarkers. The histograms display the frequencies of most frequent (>10%) selected markers in serum *(a)* and CSF *(b)* models. The biomarkers retained in final best models are bFGF, CRP, IL-16, sFLT-1, sICAM-1, Tie-2, VEGF-C, VEGF-D in serum, and IL-15, MCP-1, sFLT-1 in CSF.

The 37 neuroinflammatory biomarkers, either in CSF or serum, were analyzed for correlation with CSF Aβ1-42, tau or p-tau181. No significant correlation was observed with Aβ1-42 after correction for multiple testing. Six CSF inflammatory markers were correlated with both CSF tau and p-tau181: IL-15, MCP-1, VEGFR-1/ sFLT-1, sICAM1, sVCAM-1, VEGF-D, together with serum IL-8 correlated with CSF p-tau181 (Table 2). Correlations of the 6 CSF inflammatory biomarkers with CSF tau are illustrated in Figure 3).

Table 2 – Neuroinflammatory biomarkers significantly correlated with AD CSF markers.

Tissue	**Biomarker**	r^2 (*p*-value)	
		***vs.* CSF tau**	***vs.* CSF p-tau181**
CSF	IL-15	0.26 (2e-9)	0.24 (1e-8)
	MCP-1	0.16 (6e-6)	0.14 (2e-5)
	sFLT-1	0.37 (1e-13)	0.32 (3e-11)
	sICAM-1	0.22 (1e-7)	0.16 (6e-6)
	sVCAM-1	0.26 (4e-9)	0.20 (4e-7)
	VEGF-D	0.18 (2e-5)	0.14 (2e-4)
serum	IL-8	*not significant*	0.09 (9e-4)

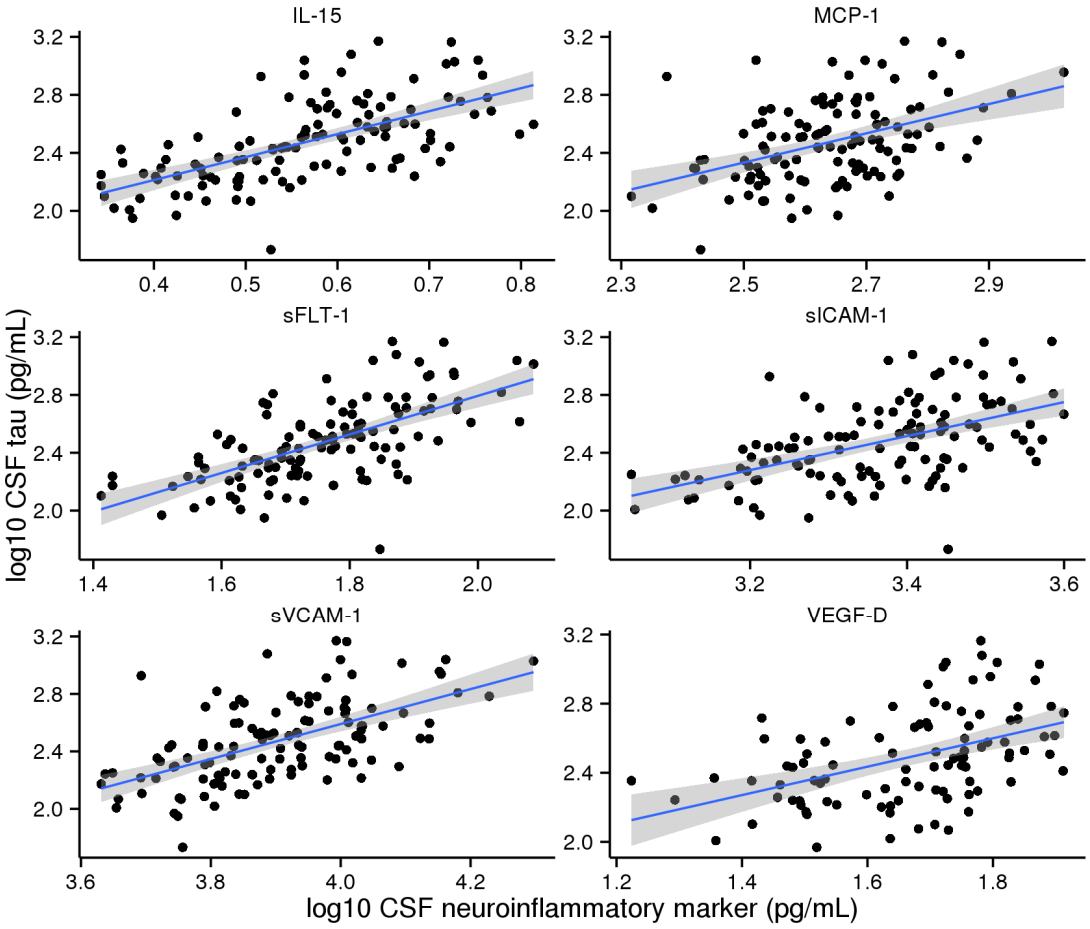


Figure 3 – Correlations between CSF neuroinflammatory and CSF tau.

Correlation of six CSF neuroinflammatory biomarkers (log_{10}-transformed concentrations, in pg/mL) with CSF tau (log_{10}-transformed concentrations, in pg/mL). Each dot represents a subject. The blue line represents the linear fit, and the gray shading its confidence interval.

The results of the linear regression models with CSF tau and CSF p-tau181 as dependent variables are summarized in Table 3 a. and 3 b respectively. The cognitive impairment status term (CDR = 0 vs. CDR > 0) was found associated in all models, confirming the association of high expression levels of CSF tau with cognitive impairment. Interaction terms between biomarker and age, sex, CDR, and APOE ε4 status were then added to the regression models and tested in an ANOVA. The only significant interaction was found between CDR category

and sFLT-1, where the correlation between CSF sFLT-1 and tau was stronger in the CDR > 0 category than in the CDR = 0 category (p = 0.04). The F-value of the CDR x sFLT-1 interaction term is 4.44 (df=1). The correlation in the CDR 0 group is r = 0.43 (r2 = 0.19, p = 0.002) vs. r = 0.67 (r2 = 0.44, p = 1.7e-10) in the CDR >0 group. No other interactions were identified.

Table 3a – Regression coefficients in linear model with CSF tau as dependent variable.

Regression term	IL-15	MCP-1	sFLT-1	sICAM-1	sVCAM-1	VEGF-D
Inflammation marker	1.406 ***	0.702 ***	1.171 ***	0.839 ***	1.006 ***	0.470 ***
Age	0.001	0.006	0.007 **	0.005	0.004	0.008 **
Sex	0.007	-0.009	-0.057	0.007	0.023	-0.004
APOEε4 status	0.125 **	0.058	0.099 *	0.100 *	0.103 *	0.089
CDR category	0.150 ***	0.183 ***	0.129 **	0.140 **	0.157 ***	0.174 ***
intercept	1.455 ***	0.083	-0.131	-0.817	-1.876 **	1.008 ***

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 3b – Regression coefficients in linear model with CSF p-tau181 as dependent variable.

Regression term	IL-15	MCP-1	sFLT-1	sICAM-1	sVCAM-1	VEGF-D
Inflammation marker	0.957 ***	0.396 **	0.836 ***	0.610 ***	0.667 ***	0.375 ***
Age	0.000	0.004	0.004 *	0.002	0.002	0.005 *
Sex	-0.004	-0.016	-0.049	-0.003	0.006	-0.010
APOEε4 status	0.060 *	0.018	0.043	0.044	0.046	0.036
CDR category	0.100 **	0.122 ***	0.083 **	0.090 *	0.105 **	0.114 **

intercept	1.112 ***	0.363	-0.028	-0.550	-1.092 *	0.730 ***

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

4. Discussion

We identified serum and CSF inflammation biomarker signatures associated with the presence of core AD pathology in older adults with normal cognition and cognitive impairment. The selected inflammatory biomarkers from serum (bFGF, CRP, IL-16, sFLT-1, sICAM-1, Tie-2, VEGF-C, and VEGF-D) and, separately, from CSF (IL-15, MCP-1, and sFLT-1) significantly improved the accuracy of classification for AD pathology, in particular in subjects with cognitive impairment. Furthermore, the CSF concentrations of six neuroinflammation markers (IL-15, MCP-1, sFLT-1, sICAM-1, sVCAM-1) were associated with the CSF tau and p-tau181 levels after controlling for several possible confounders.

Applying an approach unbiased by the clinical diagnosis, we identified distinct inflammatory biomarker signatures in serum and CSF associated with the presence of "core" AD pathology i.e. the combined presence of cerebral amyloid and tau pathology. The differences observed between the serum and CSF inflammatory profiles, while considering the blood-brain-barrier function, support the hypothesis that peripheral inflammatory activity related to AD may be at least partially independent of inflammation in the CNS. As it is based on an easily accessible tissue, the serum inflammatory marker signature may be particularly helpful for early non-invasive screening for elderly subjects at risk of cognitive decline related to AD at pre-dementia and prodromal disease stages. While an unbiased classification based on markers of cerebral amyloid, tau pathology, and neuronal injury can be used across the clinical stages (Jack et al., 2016), our results suggest that the inflammatory biomarker signatures may be particularly useful in the subjects with cognitive impairment. In the subgroup with MCI and mild dementia, adding the CSF and serum inflammation markers to the demographic metrics

improved the accuracy more markedly (by 12.5% and 13.9%, respectively; see also the Supplementary Figure) than in the participants with and without cognitive impairment considered together (improvement by 7.4% and 8.1%, respectively). Also, the differences between the AUC were significant when performed in the subgroup with cognitive impairment, but not in the whole sample of participants. These findings suggest that inflammatory biomarker signatures may improve the diagnostic accuracy of cerebral AD pathology underlying cognitive impairment in MCI and mild dementia. Independent validation is needed to evaluate their usefulness in clinical settings.

Addressing the relationships between inflammatory markers and amyloid and tau pathology, we found six CSF neuroinflammation markers to be correlated with CSF tau and ptau independently of age, gender, cognitive status, and APOEe4 status. None of the included inflammation marker was correlated with CSF Aβ1-42 levels.

Enhanced expression of mediators of inflammation has been previously described in the vicinity of amyloid plaques suggesting increased inflammatory activity as a consequence of accumulating amyloid pathology (Bacher et al., 2010; Calsolaro and Edison, 2016). Furthermore, sustained neuroinflammation may contribute to the development of amyloid pathology by stimulating the expression of inflammatory mediators that have been shown to increase amyloid precursor protein and amyloid production (Heneka et al., 2015; Popp et al., 2009). Cerebral amyloid accumulation was shown to increase under inflammatory conditions in animals (Calsolaro and Edison, 2016). However, recent studies have found that, while glial inhibition or depletion may prevent neuronal loss, it may have no substantial effects on cerebral amyloid accumulation (Coma et al., 2010; Spangenberg et al., 2016) suggesting that amyloid production in AD may much more depend on other mechanisms. Also, a few studies assessing single inflammation markers in the CSF have found significant associations of these markers with Aβ1-42 levels in subjects with normal Aβ1-42 only (Alcolea et al., 2015;

Henjum et al., 2016). In line with these studies, we observed no correlation between inflammation markers and the CSF Aβ1-42 levels.

Evidence from animal AD models suggests that both localized microglia activation related to cerebral amyloid pathology and CNS inflammatory response to systemic inflammation can exacerbate the development of tau pathology and may correlate with the spread of pathological tau in the brain (Ghosh et al., 2013; Kitazawa et al., 2005; Maphis et al., 2015) (Lee et al., 2010),(Fang et al., 2016). Microglial activation precedes the development of tau pathology while early immunosuppression in tau transgenic mice results in attenuated tau pathology, reduced neuronal and synaptic loss, and increased lifespan (Jiang et al., 2016; Yoshiyama et al., 2007). Also, studies using different models of immune deficiency in AD transgenic mice found reduced tau hyperphosphorylation in relation to suppressed inflammatory activity (Li, Yu et al. 2015).

Among the markers of neuroinflammation included in our study, one serum marker (IL-8) was associates with the CSF ptau and six CSF markers (IL-15, MCP-1, sFLT-1, sICAM-1, sVCAM-1) were associated with the CSF ptau and tau levels suggesting the implication of these molecules in tau hyperphosphorylation and neuronal injury. IL-8 is a chemokine and angiogenesis promoter produced by macrophages but also by other cell types such as epithelial and endothelial cells. IL-8 has been reported to be increase in plasma and CSF of patients with clinically diagnosed AD (Wennstrom et al., 2015), but other studies found no association (Delaby et al., 2015; Swardfager et al., 2010) or even decreased levels (Hesse et al., 2016) in AD dementia. In our study we observed only a relatively weak association the serum IL-8 with p-tau181 levels after controlling for confounders. IL-15 is a pro-inflammatory cytokine which was shown to promote microglial activation through the NFκB, p38, and ERK1⁄2 pathways, thereby enhancing the production of pro-inflammatory cytokines and growth factors (Gomez-Nicola et al., 2010). IL-15 also regulates T and B lymphocyte

activity and displays neurotrophic, anti-apoptic and pro-neurogenesis effects (Bishnoi et al., 2015). Lower serum IL-15 levels were found in patients with AD compared to healthy subjects and to subjects with vascular dementia (Rentzos et al., 2007), while in the CSF higher IL-15 concentrations have been observed in subjects with AD and fronto-temporal dementia compared to patients with non-inflammatory neurological disorders (Rentzos et al., 2006).

MCP-1 is a key chemokine involved in monocyte/macrophage migration during inflammatory processes, which can be produced by different cell types including astrocytes and microglia (Barber et al., 2015; Deshmane et al., 2009). MCP-1 serum and CSF levels have been reported to be increased in MCI and AD dementia (Galimberti et al., 2006a; Galimberti et al., 2006b).

Cell Adhesion Molecules (CAMs), including sVCAM-1 and sICAM-1 may be considered as biomarkers of endothelial dysfunction in AD (Grammas, 2011; Huang et al., 2015). While VCAM-1 is expressed only by endothelial cells, ICAM-1 is also expressed by leukocytes and astrocytes (Huang et al., 2015; Rentzos et al., 2004) and it has been found within amyloid plaques (Verbeek et al., 1994). Levels of both VCAM-1 and ICAM-1 have been reported to be elevated in patients with clinically diagnosed AD dementia (Huang et al., 2015; Rentzos et al., 2004).

VEGF is a family of molecules that bind to tyrosine kinase receptors such as VEGFR-1/ sFLT-1, and play a key role in angiogenesis, but also in promoting neurogenesis in the dentate gyrus in the hippocampus (Carmeliet and Storkebaum, 2002; Dal Pra et al., 2014). CSF VEGF levels have been previously found to be elevated among patients with AD dementia (Tarkowski et al., 2002). VEGF is expressed by neurons, microglia, astrocytes and endothelial cells, and was found within diffuse perivascular amyloid plaques in the brains of patients with AD (Merrill and Oldfield, 2005; Thirumangalakudi et al., 2006). It has been hypothesized that

VEGF is secreted following stimulation by Aβ and may indicate a compensatory mechanism for the compromised vasculature and perfusion in the AD brain (Patel et al., 2010) (Salomon-Zimri et al., 2016).

In this context, our findings of highly significant correlations between CSF ptau181 and tau levels, and six CSF markers of cytokine mediated inflammation, vascular injury, and angiogenesis support the hypothesis that increased cerebral inflammatory activity and microvascular pathology may contribute to tau hyperphosphorylation and neuronal injury in AD. While further studies including experimental approaches are needed to understand the precise underlying mechanisms, our results suggest that specific neuroinflammatory processes indicated by these markers could represent therapeutic targets in the future to prevent or slow down the development of tau pathology and neurodegeneration in early AD. The preliminary findings on associations between some inflammatory markers and global cognitive performance further suggest that inflammation may be related to the severity of cognitive impairment in MCI and mild dementia.

Strengths of this study are the large panel of markers known to play a role in the immune response in the CNS including cytokines, chemokines and markers of inflammation related to vascular injury and angiogenesis. Further, the parallel assessment of both blood and CSF markers of inflammation in the same participants while considering BBB function provides insights on the relationships between peripheral and CNS inflammation associated to AD pathology.

A limitation of this study is the lack of longitudinal biomarker measures and the non-inclusion of more severe dementia cases. Some of the measured inflammatory markers might increase steadily during disease progression or temporarily at the pre-clinical and early clinical disease stages (Calsolaro and Edison, 2016). The identified signatures might be specific for early stage AD, and may differ from signatures in more advanced clinical stages, or from signatures

associated with a rapid cognitive decline. While the primary aim of this study was to identify serum and CSF inflammation markers associated with core AD pathology, the results suggest that the identified inflammatory signatures may represent useful markers to improve diagnosis accuracy and prediction of further cognitive decline. The serum inflammatory marker signature of AD may be particularly helpful for early non-invasive screening for elderly subjects at risk of developing AD dementia and for identifying potential participants for targeted interventions at pre-dementia disease stages. Further studies including longitudinal follow-up and independent sample validation are needed to address these aspects.

Together, the results of this study provide evidence that inflammation is part of the AD pathology at early clinical stages. Specific combinations of serum and CSF inflammation markers improve prediction of cerebral AD pathology in older adults, in particular in subjects with cognitive impairment. Independent sample validation and longitudinal clinical follow-up are needed to evaluate the usefulness of inflammatory biomarker signatures in clinical settings. Cytokine mediated inflammation, vascular injury, and angiogenesis as reflected by CSF markers are closely related to markers of cerebral tau pathology suggesting involvement in tau hyperphosphorylation and neuronal injury. These relationships may represent potential intervention targets to reduce neurodegeneration in AD.

5. Acknowledgement

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6. Markers of neuroinflammation associated with Alzheimer's disease pathology in older adults – Supplementary tables and figures

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Supplementary table 1

Demographics and biochemical markers by CSF profile categories.

	All (n = 120)	**Non-AD CSF biomarker profile (n=78)**	**AD CSF biomarker profile (n=42)**
Age (years), mean (SD)	70.4 (7.9)	68.4 (8.3)	74.1 (5.6)*
Gender, No. (%) of Males	43 (35.83%)	25 (32.05%)	18 (42.86%)
Education years, mean (SD)	12.4 (2.6)	12.5 (2.7)	12.1 (2.4)
MMSE scale, mean (SD)	26.9 (3.1)	27.8 (2.3)	25.2 (3.7)*
APOE ε4 carriers, No. (%)	37 (30.83%)	13 (16.67%)	24 (57.14%)*
CSF Aβ 1-42 (pg/mL), mean (SD)	847.4 (265.1)	979.9 (196.4)	601.2 (190.0)*
CSF p-tau181 (pg/mL), mean (SD)	62.0 (35.2)	46.7 (13.4)	90.3 (44.8)*
CSF tau (pg/mL), mean (SD)	371.3 (278.6)	235.1 (104.2)	624.2 (322.4)*
Albumin ratio, mean (SD)	6.1 (2.4)	5.9 (2.4)	6.4 (2.3)
Inflammation markers in serum			
BFGF (pg/mL), mean (SD)	4.5 (4.7)	4.7 (4.8)	4.2 (4.4)
CRP (μg/mL), mean (SD)	2.5 (4.1)	2.7 (3.8)	2.1 (4.6)
Eotaxin (pg/mL), mean (SD)	169.6 (68.2)	166.4 (67.0)	176.5 (71.7)
Eotaxin-3 (pg/mL), mean (SD)	37.6 (37.9)	32.1 (15.4)	49.6 (62.7)
IFNγ (pg/mL), mean (SD)	10.2 (12.6)	9.8 (13.4)	10.8 (11.1)
IL-12/IL-23p40 (pg/mL), mean (SD)	161.8 (77.5)	156.1 (79.5)	172.1 (73.5)
IL-15 (pg/mL), mean (SD)	3.0 (0.6)	3.0 (0.6)	3.0 (0.7)
IL-16 (pg/mL), mean (SD)	227.7 (72.7)	231.5 (80.7)	220.8 (55.7)

IL-6 (pg/mL), mean (SD)	4.9 (44.0)	0.8 (0.6)	12.4 (73.8)
IL-7 (pg/mL), mean (SD)	29.3 (9.9)	29.8 (10.4)	28.6 (9.0)
IL-8 (pg/mL), mean (SD)	15.3 (7.7)	14.8 (5.2)	16.1 (10.8)
IP-10 (pg/mL), mean (SD)	375.0 (239.5)	360.5 (221.8)	406.3 (276.3)
MCP-1 (pg/mL), mean (SD)	343.0 (130.7)	339.5 (133.0)	350.6 (127.8)
MCP-4 (pg/mL), mean (SD)	179.8 (90.3)	183.7 (94.9)	171.5 (80.6)
MDC (pg/mL), mean (SD)	1022.9 (313.8)	1073.6 (345.8)	913.3 (193.9)*
MIP-1α (pg/mL), mean (SD)	24.0 (10.6)	23.6 (11.4)	24.9 (8.6)
MIP-1β (pg/mL), mean (SD)	109.2 (51.5)	114.8 (50.9)	97.3 (51.8)
pIGF-1R (pg/mL), mean (SD)	28.3 (7.4)	27.4 (6.7)	29.8 (8.2)
SAA (μg/mL), mean (SD)	7.6 (19.5)	9.2 (23.9)	4.8 (4.5)
sFLT-1 (pg/mL), mean (SD)	114.9 (35.1)	112.0 (38.3)	120.2 (28.1)
sICAM-1 (ng/mL), mean (SD)	372.2 (89.4)	379.1 (89.8)	359.7 (88.2)
sVCAM-1 (ng/mL), mean (SD)	576.2 (130.4)	572.8 (134.6)	582.3 (123.9)
TARC (pg/mL), mean (SD)	267.1 (185.8)	263.0 (183.7)	276.0 (193.9)
Tie-2 (ng/mL), mean (SD)	6.3 (1.6)	6.5 (1.6)	6.1 (1.7)
TNF α (pg/mL), mean (SD)	2.9 (1.1)	3.0 (1.3)	2.8 (0.7)
VEGF (pg/mL), mean (SD)	142.5 (114.4)	148.2 (106.1)	132.2 (128.9)
VEGF-C (pg/mL), mean (SD)	511.9 (168.9)	523.7 (163.5)	490.7 (178.1)
VEGF-D (pg/mL), mean (SD)	813.6 (268.1)	760.8 (211.3)	909.1 (330.1)*
Inflammation markers in CSF			
CRP (ng/mL), mean (SD)	7.2 (14.1)	7.9 (12.8)	6.0 (16.3)
IL-12/IL-23p40 (pg/mL), mean (SD)	5.8 (2.1)	5.8 (2.3)	5.6 (1.5)
IL-15 (pg/mL), mean (SD)	3.8 (1.0)	3.6 (1.0)	4.2 (0.9)*

IL-16 (pg/mL), mean (SD)	13.2 (5.1)	13.0 (3.6)	13.7 (7.1)
IL-6 (pg/mL), mean (SD)	1.2 (0.9)	1.2 (0.8)	1.3 (1.0)
IL-7 (pg/mL), mean (SD)	1.4 (0.6)	1.4 (0.6)	1.5 (0.6)
IL-8 (pg/mL), mean (SD)	41.9 (14.7)	39.9 (9.1)	45.4 (21.1)
IP-10 (pg/mL), mean (SD)	596.2 (320.5)	601.7 (361.9)	586.1 (229.7)
MCP-1 (pg/mL), mean (SD)	453.4 (135.7)	423.7 (121.6)	507.8 (144.6)*
MCP-4 (pg/mL), mean (SD)	5.4 (3.3)	5.0 (3.2)	6.0 (3.3)
MDC (pg/mL), mean (SD)	33.4 (21.4)	34.5 (22.8)	31.5 (18.9)
MIP-1α (pg/mL), mean (SD)	20.6 (6.6)	20.2 (6.6)	21.4 (6.6)
MIP-1β (pg/mL), mean (SD)	14.4 (4.5)	14.4 (4.8)	14.6 (3.7)
pIGF-1R (pg/mL), mean (SD)	80.2 (29.6)	76.1 (29.0)	87.7 (29.4)*
SAA (ng/mL), mean (SD)	2.0 (5.8)	2.2 (7.0)	1.4 (1.8)
sFLT-1 (pg/mL), mean (SD)	60.3 (19.1)	54.1 (15.3)	71.7 (20.4)*
sICAM-1 (ng/mL), mean (SD)	2.4 (0.7)	2.3 (0.7)	2.6 (0.5)*
sVCAM-1 (ng/mL), mean (SD)	8.4 (2.8)	7.9 (2.5)	9.3 (3.1)*
TARC (pg/mL), mean (SD)	4.0 (2.2)	4.0 (2.4)	4.2 (1.9)
VEGF (pg/mL), mean (SD)	4.3 (1.0)	4.2 (0.9)	4.3 (1.1)
VEGF-D (pg/mL), mean (SD)	44.3 (17.2)	41.5 (15.9)	49.5 (18.4)*

*statistically different ($p \leq 0.05$) from the group with Non-AD CSF profile, using *t*-tests for continuous variables and binomial proportion tests for categorical variables.

APOEε4 = Apolipoprotein E ε4 allele; MMSE = Mini Mental State Examination

Supplementary table 2

Correlation between neuroinflammatory markers and MMSE in cognitively impaired subjects.

Biomarker	Serum			CSF		
	r	r^2	p	r	r^2	p
BFGF	0.1943	0.03775	0.1097	NA	NA	NA
CRP	-0.1983	0.03933	0.09493	-0.2839	0.08058	0.01567
Eotaxin	-0.2353	0.05537	0.1197	NA	NA	NA
Eotaxin-3	0.02923	0.0008544	0.8636	NA	NA	NA
IFNγ	-0.04643	0.002156	0.7006	NA	NA	NA
IL-12/IL-23p40	-0.1447	0.02092	0.2254	-0.2464	0.06072	0.03693
IL-15	-0.2275	0.05174	0.05642	-0.1131	0.01279	0.3443
IL-16	-0.2652	0.07033	0.02436	-0.3884	0.1509	0.0007468
IL-6	0.002301	5.294e-06	0.9886	0.07275	0.005293	0.5465
IL-7	0.03365	0.001133	0.779	0.1058	0.01119	0.4555
IL-8	-0.3079	0.09478	0.008516	-0.1044	0.0109	0.3828
IP-10	0.2255	0.05087	0.1363	-0.1981	0.03926	0.09524
MCP-1	0.05224	0.002729	0.7333	-0.101	0.01019	0.3988
MCP-4	-0.1211	0.01465	0.4283	0.07942	0.006307	0.6502
MDC	0.06647	0.004418	0.6644	0.02707	0.0007327	0.8978

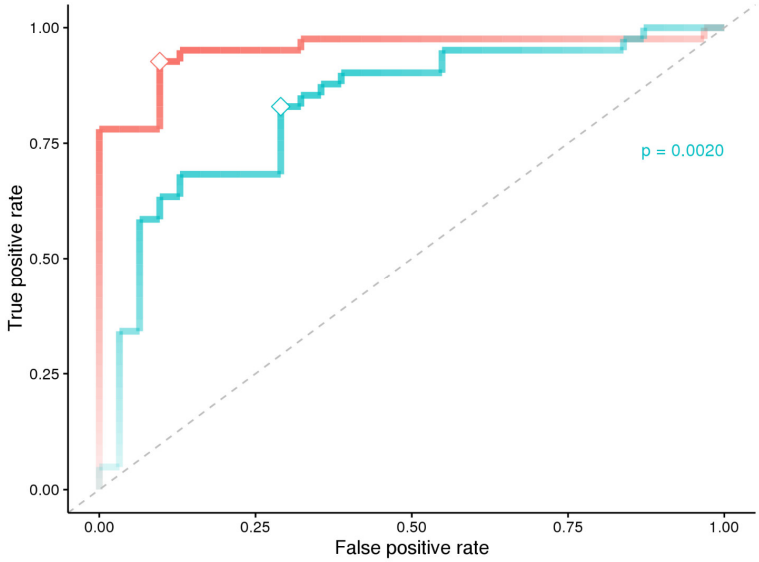
Biomarker	Serum			CSF		
	r	r^2	p	r	r^2	p
MIP-1α	0.1861	0.03462	0.2921	-0.224	0.05016	0.07521
MIP-1β	0.05514	0.00304	0.719	0.0443	0.001963	0.7117
pIGF-1R	0.1275	0.01625	0.2859	-0.211	0.04452	0.07523
SAA	-0.03499	0.001224	0.7704	-0.3402	0.1157	0.003457
SFLT-1	-0.09135	0.008344	0.4454	0.04022	0.001618	0.7373
SICAM-1	0.05467	0.002989	0.6483	-0.2917	0.08507	0.01292
SVCAM-1	0.02821	0.0007958	0.814	-0.03917	0.001534	0.7439
TARC	0.03566	0.001271	0.8161	-0.1504	0.02261	0.2873
TIE-2	-0.006862	4.708e-05	0.9544	NA	NA	NA
TNF α	-0.1077	0.0116	0.3679	NA	NA	NA
VEGF	0.1595	0.02544	0.1808	-0.1687	0.02845	0.1567
VEGF-C	0.03197	0.001022	0.7898	NA	NA	NA
VEGF-D	-0.1783	0.03179	0.134	-0.06774	0.004588	0.6134

Supplementary table 3

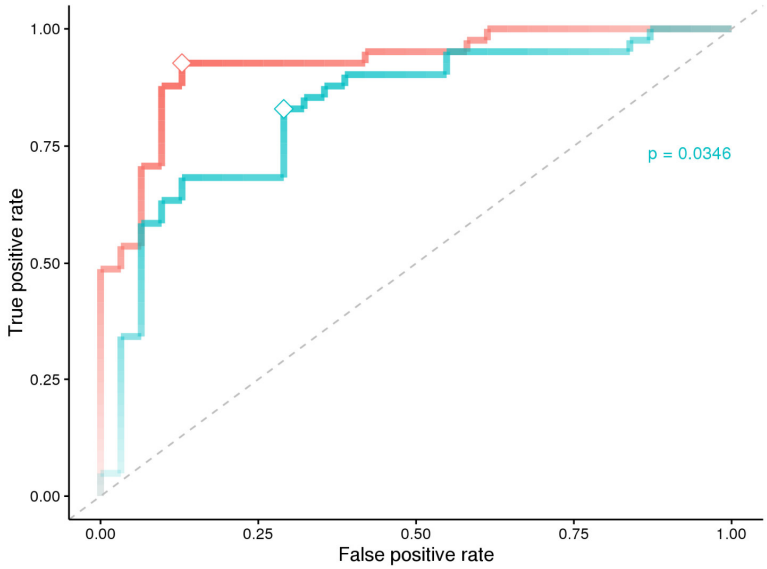
Fluid	Biomarker	CSF tau		CSF p-tau		CSF Aβ1-42	
		r2	p	r2	p	r2	p
CSF	CRP	0.0003235	0.846	0.001865	0.6409	0.00955	0.2904
CSF	IL_12/IL_23P40	0.01226	0.2306	0.009082	0.3026	0.03764	0.0345
CSF	IL-15	0.2654	2.039e-09	0.245	1.05e-08	0.002249	0.6086
CSF	IL-16	0.01716	0.1556	0.01479	0.1877	0.001367	0.6897
CSF	IL-6	0.0002887	0.8551	0.001645	0.6628	0.01254	0.2273
CSF	IL-7	0.001604	0.7243	0.01029	0.3706	0.006242	0.486
CSF	IL-8	0.02897	0.06421	0.01471	0.1889	0.01402	0.1997
CSF	IP-10	0.006924	0.3683	0.005959	0.404	0.002767	0.5699
CSF	MCP-1	0.1621	5.649e-06	0.142	2.397e-05	0.05423	0.01082
CSF	MCP-4	0.02436	0.2791	0.01007	0.488	0.02086	0.3169
CSF	MDC	0.003253	0.6971	0.001118	0.8196	8.665e-05	0.9494
CSF	MIP-1A	0.001327	0.7176	0.002558	0.6155	0.0008347	0.7743
CSF	MIP-1B	0.02877	0.06515	0.03654	0.0373	0.00127	0.7004
CSF	PIGF-1R	0.01279	0.2207	0.005253	0.4335	0.03163	0.05299
CSF	SAA	0.0004854	0.812	0.0003939	0.8304	0.003962	0.4965
CSF	SFLT-1	0.3742	1.461e-13	0.3159	2.921e-11	0.007829	0.3386
CSF	SICAM-1	0.2159	1.022e-07	0.1608	6.2e-06	0.004468	0.4701
CSF	SVCAM-1	0.2576	3.847e-09	0.1971	4.252e-07	0.007408	0.352
CSF	TARC	0.009188	0.3977	0.01015	0.3739	0.01018	0.3732
CSF	VEGF	0.01739	0.1528	0.01547	0.1777	0.03451	0.04311
CSF	VEGF-D	0.1766	1.824e-05	0.1369	0.000191	0.000304	0.8654
SERUM	bFGF	0.008102	0.3431	0.01401	0.2118	0.0006154	0.7942
SERUM	CRP	0.0007429	0.7695	2.133e-05	0.9604	0.02808	0.06974
SERUM	EOTAXIN	0.03644	0.09197	0.06677	0.02149	0.07626	0.01376
SERUM	EOTAXIN-3	0.02447	0.2134	0.06269	0.04425	0.01563	0.321
SERUM	IFN-G	0.01741	0.158	0.01226	0.2368	0.004118	0.4937
SERUM	IL-12/IL-23P40	0.001056	0.7268	1.358e-05	0.9684	2.732e-05	0.9552
SERUM	IL-15	0.004106	0.4925	1.726e-05	0.9645	0.0009366	0.7433
SERUM	IL-16	0.004112	0.4903	0.01189	0.2398	0.0001476	0.8961
SERUM	IL-6	0.001357	0.7726	0.02911	0.1776	0.016	0.3192
SERUM	IL_7	0.003842	0.5049	0.000976	0.737	0.002625	0.5816

SERUM	IL_8	0.01972	0.1294	0.09044	0.0009367	0.004297	0.4806
SERUM	IP_10	0.01147	0.3476	0.001015	0.7805	0.0005459	0.8381
SERUM	MCP_1	0.03958	0.0788	0.01902	0.2255	0.007945	0.4347
SERUM	MCP_4	0.02464	0.1671	0.01643	0.2602	0.0002622	0.8874
SERUM	MDC	0.02151	0.1972	0.02478	0.1659	0.07169	0.01705
SERUM	MIP_1A	0.0002669	0.9023	0.009841	0.4547	0.02668	0.2164
SERUM	MIP_1B	0.001628	0.7241	4.15e-05	0.9551	0.01484	0.2848
SERUM	PIGF-1R	0.05444	0.011	0.03007	0.06039	0.001453	0.6819
SERUM	SAA	0.005115	0.4415	0.00115	0.7154	0.0155	0.1791
SERUM	SFLT-1	0.01064	0.2664	0.001217	0.7077	0.002335	0.6033
SERUM	SICAM-1	0.002597	0.5836	0.001625	0.6647	0.02377	0.09552
SERUM	SVCAM-1	0.01487	0.1883	0.02065	0.1205	0.03433	0.04457
SERUM	TARC	0.002146	0.6852	0.001686	0.7194	0.004668	0.5497
SERUM	TIE-2	0.001901	0.6392	6.178e-07	0.9933	0.03242	0.05104
SERUM	TNF-A	0.007494	0.3513	0.001869	0.6421	0.002515	0.5897
SERUM	VEGF	0.0024	0.5983	0.005749	0.4145	0.0113	0.252
SERUM	VEGF-C	0.00106	0.7263	0.002456	0.594	0.009107	0.304
SERUM	VEGF-D	0.05526	0.01039	0.0391	0.03184	0.02879	0.06625

(a)



(b)


1.00
0.75
0.50
0.25
0.00
True positive rate
0.00
0.25
0.50
0.75
1.00
False positive rate
p = 0.0346

Supplementary Figure – ROC curves of the serum *(a)* and CSF *(b)* models predictive of biomarker CSF profile in subjects with cognitive impairment.

The ROC curves of the LASSO models including neuroinflammatory biomarkers (in red) are compared with the ROC curves of the reference LASSO models (in blue) in the sub-population of 72 subjects with cognitive impairment (CDR > 0). The opacity of the curves is proportional to the accuracy of the models. The diamonds indicate the selected most accurate models. The p-values on the graphs indicate the significance of the differences of AUC. The biomarkers models had a ROC AUC of 0.96 [0.89 – 0.99] in serum and 0.93 [0.85 – 0.97] in CSF.

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HIGHLIGHTS:

- Distinct serum and CSF inflammation signatures are associated with AD pathology.
- Serum and CSF inflammation markers improve the classification accuracy for AD.
- Six CSF inflammation markers were associated with tau pathology and neuronal injury.