

RESEARCH ARTICLE

Contribution of CSF biomarkers to early-onset Alzheimer's disease and frontotemporal dementia neuroimaging signatures

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Funding information

Forskningsrådet om Hälsa, Arbetsliv och Välfärd, Grant/Award Number: 2018-02532; Fundacio Marató de TV3, Grant/Award Number: 20143810; Generalitat de Catalunya, Grant/Award Numbers: SLT002/16/00408, SLT008/18/00061, SLT002/16/00329; European Research Council, Grant/Award Number: 681712; Hjärnfonden, Grant/Award Number: FO2017-0243; Hospital Clínic Barcelona; Spanish Ministry of Economy and Competitiveness, Grant/Award Number:

Abstract

Prior studies have described distinct patterns of brain gray matter and white matter alterations in Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD), as well as differences in their cerebrospinal fluid (CSF) biomarkers profiles. We aim to investigate the relationship between early-onset AD (EOAD) and FTLD structural alterations and CSF biomarker levels. We included 138 subjects (64 EOAD, 26 FTLD, and 48 controls), all of them with a 3T MRI brain scan and CSF biomarkers available (the 42 amino acid-long form of the amyloid-beta protein [A β 42], total-tau protein [T-tau], neurofilament light chain [NfL], neurogranin [Ng], and 14-3-3 levels). We used FreeSurfer and FSL to obtain cortical thickness (CTh) and fraction anisotropy (FA) maps. We studied group differences in CTh and FA and described the "AD signature" and "FTLD signature." We tested multiple regression models to find which CSF-biomarkers better explained each disease neuroimaging signature. CTh and FA maps

Neus Falgàs, Mariona Ruiz-Peris, Albert Lladó, and Raquel Sánchez-Valle authors contributed equally to this work.

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PI14/00282; Swedish Alzheimer Foundation, Grant/Award Number: AF-742881; Swedish State Support for Clinical Research, Grant/Award Numbers: ALFGBG-715986, ALFGBG-720931

corresponding to the AD and FTLD signatures were in accordance with previous literature. Multiple regression analyses showed that the biomarkers that better explained CTh values within the AD signature were A β and 14-3-3; whereas NfL and 14-3-3 levels explained CTh values within the FTLD signature. Similarly, NfL levels explained FA values in the FTLD signature. Ng levels were not predictive in any of the models. Biochemical markers contribute differently to structural (CTh and FA) changes typical of AD and FTLD.

KEYWORDS

Alzheimer's disease, biological markers, Frontotemporal Dementia, magnetic resonance imaging

1 | INTRODUCTION

Early-onset dementia (EOD) is usually defined by a clinical onset under 65 and can reach up to the 5–10% of patients with dementia. Alzheimer's disease (AD) is the most common cause of EOD, followed by frontotemporal lobar degeneration (FTLD; Garre-Olmo, Genís Batlle, del Mar Fernández, et al., 2010). Early-onset AD (EOAD) is characterized by a faster disease progression and atypical presentations (nonamnestic symptoms) overlapping with other neurodegenerative dementias such as FTLD making the diagnosis more challenging (Koedam, Lauffer, van der Vlies, et al., 2010; Wattmo & Wallin, 2017). Thus, the use of neuroimaging and biochemical biomarkers is especially suitable in EOD in order to establish an early and accurate diagnosis (Falgàs, Tort-Merino, Balasa, et al., 2019).

Several studies have aimed to determine the different profiles of cerebrospinal fluid (CSF) biomarkers in different neurodegenerative diseases such as AD or FTLD (Blennow & Zetterberg, 2018). Some of these biomarker profiles have been well described while other novel biomarkers are still under investigation. Decreased amyloid-beta protein 42 (A β 42) with increased total tau (T-tau) and phosphorylated tau (P-tau) levels define the typical AD biochemical profile (Albert, DeKosky, Dickson, et al., 2011; Mattson, 2017; McKhann, Knopman, Chertkow, et al., 2011). Regarding novel biomarkers, neurofilament light chain (NfL) has been proposed as a nonspecific neurodegeneration marker. Increased levels of NfL have been reported in FTLD, as well as in AD and other neurodegenerative disorders (i.e., amyotrophic lateral sclerosis or multiple sclerosis). CSF NfL levels have proved especially useful differentiating FTLD from early-onset AD given that NfL levels in AD are lower in early onset compared to those in late onset presentations (Alcolea, Vilaplana, Suárez-Calvet, et al., 2017; Olsson, Portelius, Cullen, et al., 2019; Portelius et al., 2018; Sjögren, Rosengren, Minthon, et al., 2000). Neurogranin (Ng) is a synaptic (dendritic) marker that has been suggested to be specific for AD although increased levels are also found in Creutzfeldt–Jakob diseases (Blennow, Diaz-Lucena, Zetterberg, et al., 2019; Gaetani, Blennow, Calabresi, et al., 2019; Wellington et al., 2016). The 14-3-3 protein has been extensively studied in Creutzfeldt–Jakob disease, but its participation on the AD neuropathological process has also been described (Burkhard, Sanchez,

Landis, et al., 2001; Chohan et al., 2010; McFerrin, Chi, Cutter, et al., 2017). Furthermore, previous studies have suggested that some of these biomarkers, as NfL or Ng, could provide information about the disease prognosis in AD and FTLD, respectively (Ljubenkov et al., 2018; Rohrer et al., 2016; Scherling et al., 2014).

Neuroimaging using Magnetic Resonance Imaging (MRI) has been widely used to describe cortical thickness (CTh) and white matter (WM) loss patterns in AD and FTLD as well as to find differential trajectories along the different disease stages (Canu et al., 2017; Möller, Hafkemeijer, Pijnenburg, et al., 2015; Moreno et al., 2013; Sala-Llonch et al., 2015).

The relationship between AD neuroimaging features and classical AD biochemical markers and their reciprocal influence have been studied during both the clinical and preclinical phases of the disease (Sala-Llonch et al., 2015). However, studying the influence of new biomarkers is more challenging as the trajectories have been poorly described and they might interact with those already reported, possibly giving nontrivial relationships. In this sense, how the different CSF biomarkers might explain or contribute to each disease atrophy pattern is still uncertain (Idland et al., 2017; Pegueroles, 2017).

In this context, our goals were (a) to provide a descriptive analysis of CSF-biomarker levels and structural patterns (CTh, hippocampal volume, and FA) in early-onset AD and FTLD, (b) to study the relationship between early-onset AD and FTLD brain structural measures and CSF-biomarkers levels, and (c) to perform a multivariate approach to evaluate which biomarkers better explained the characteristic structural alterations associated with each disease (i.e., disease signatures).

2 | MATERIALS AND METHODS

2.1 | Participants

One hundred thirty-eight subjects with disease onset under 65 were evaluated at the Alzheimer's Disease and Other Cognitive Disorders Unit at Hospital Clínic de Barcelona and were enrolled on this cross-sectional study from 2009 to 2016. All subjects underwent a complete neurological and neuropsychological evaluation, 3T brain MRI

scan and a spinal tap for the determination of CSF biomarkers. Subjects were classified into three groups:

- AD group ($n = 64$): All EOAD patients fulfilled the National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic criteria for MCI due to AD or mild AD dementia and Mini-Mental State Examination (MMSE) ≥ 18 (Albert et al., 2011; McKhann et al., 2011). All subjects had a typical AD CSF biomarker pattern. Both early sporadic AD ($n = 52$) and autosomal dominant AD (ADAD) ($n = 12$) were included.
- FTD group ($n = 26$): Ten behavioral variant of FTD (bvFTD) patients, eight nonfluent variant for primary progressive aphasia (nfvPPA) and eight semantic variant of primary progressive aphasia (svPPA) patients were included (Rascovsky et al., 2011; Gorno-Tempini et al., 2011). Ten cases were genetic cases (four carried the C9ORF72 expansion, two MAPT mutations, and four GRN mutations). All FTLN were at mild phases of the disease (MMSE ≥ 18) at inclusion.
- Healthy controls (CTR) ($n = 48$): healthy adults (age < 65 years old) with no cognitive complaints, cognitive performance within normative range and normal levels of AD CSF biomarkers.

The study was approved by the Hospital Clinic Barcelona Ethics Committee and all participants gave written informed consent.

2.2 | CSF biomarkers

- Commercially available single-analyte enzyme-linked immunosorbent assay (ELISA) kits were used to determine levels of CSF A β 42, T-tau and P-tau (INNOTEST, Fujirebio Europe N.V., Gent, Belgium), NFL (IBL International, Hamburg, Germany) and 14-3-3 (CircuLex, MBL International Corporation, Woburn, MA) at the Alzheimer's Disease and Other Cognitive Disorders Unit Laboratory, Barcelona. The following CSF cut-off values were used in order to classify the subjects to NIA-A criteria as amyloid positive 550 pg/ml (CSF samples measured before February 2016) and 750 pg/ml (for those measured after February 2016, due to changes in the commercial kits), or neuronal injury positive (T-tau >385 pg/ml and/or P-tau 65 pg/ml). Cut-offs were obtained based on internal controls. CSF Ng concentration was measured using an in-house ELISA based on the monoclonal antibody Ng7 (epitope including amino acids 52–65 on Ng) at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden (Kvartsberg et al., 2015; Willemse, De Vos, Herries, et al., 2018). The intracoefficient variation (CV) was 0.5–3% and the inter-CV 5–8% for NFL, Ng and 14-3-3 biomarkers. All 138 participants had CSF A β , T-tau, and P-tau levels available. NFL levels were available in 133 subjects, Ng in 104, and 14-3-3 in 94.

2.3 | MRI acquisition

All participants were examined in the same 3T MRI scanner (Magnetom Trio Tim, Siemens Medical Systems, Germany). A high-

resolution 3D structural data set (T1-weighted, MP-RAGE, repetition time = 2,300 ms, echo time = 2.98 ms, 240 slices, field-of-view = 256 mm, voxel size = $1 \times 1 \times 1$ mm) and a diffusion weighted echo-planar imaging (EPI) sequence (30 directions + b0 image, with two repeated acquisitions, TR = 7,600 ms, TE = 89 ms, 60 slices, distance factor = 0%, FOV = 250 mm, matrix size = 122×122 , voxel size = $2 \times 2 \times 2$ mm) were acquired for all subjects.

2.4 | Statistical analysis of demographics and CSF biomarkers levels

We first obtained group descriptive data using the median and inter-quartile range for each CSF biomarker within each group. Shapiro-Wilk test for normality were done for each diagnostic group. Group comparisons were analyzed using chi-square for gender or Kruskal-Wallis tests for the rest of the variables. The significance threshold was set at a Bonferroni corrected p level of .05 to adjust for multiple comparisons (corrected p threshold = .0018).

Additionally, we performed additional analyses in order to compare the subgroup of bvFTD subjects ($N = 10$) with the rest of the FTLN patients. These were done also through Kruskal-Wallis tests.

2.5 | Cortical thickness processing and analysis

CTh processing and vertex-wise statistical analyses were performed using FreeSurfer v6.0.0 (<https://surfer.nmr.mgh.harvard.edu/>). The entire pipeline is fully explained elsewhere and includes a set of methods applied to the T1-weighted MRI images to generate brain surfaces and CTh maps, calculated as the closest distance between the gray/WM surface to the pial surface at each vertex of the tessellated surface (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000). Before statistics, individual CTh maps were registered to a common space and smoothed using a FWHM of 15 mm.

Using the vertex-wise CTh data, we performed a set of analyses using general linear models (GLMs). We first evaluated group differences, using age as covariate. Then, for each biomarker, we computed the correlation between the biomarker levels and CTh within each group. Results were corrected for multiple comparisons using monte-carlo simulations, and setting a threshold of $p < .05$ for cluster significance.

2.6 | Hippocampal volumes

Since the hippocampus is the main subcortical structure affected in AD we also assessed the hippocampal volume. We used the automated segmentation from FreeSurfer to obtain measures of hippocampal volume (Fischl et al., 2002). We calculated normalized hippocampal volume for each subject, by averaging left and right hippocampi and dividing by the total intracranial volume. We then calculated group differences and correlations with biomarker levels in hippocampal volume in R (<https://www.r-project.org/>)

2.7 | DTI processing and analysis

DTI processing and voxel-wise statistical analyses were performed with FSL v5.0.11 (<https://fsl.fmrib.ox.ac.uk/fsl>). Diffusion weighted images were first registered, using the B0 image as a reference volume, and corrected for motion and for eddy current effects. Then, nonbrain tissue was removed using FSL's Brain Extraction Tool, and FA maps were obtained using the FMRIB Diffusion Toolbox. Tract-Based Spatial Statistics (TBSS) was used for voxel-wise statistical analysis of FA maps (Smith, 2002; Smith et al., 2006). Basically, within the TBSS protocol, nonlinear transforms were first applied using FNIRT to obtain FA images aligned to standard space and the resulting images were merged into single 4D image. Then, the mean of all FA images was fed into a skeletonization protocol obtaining the group mean FA skeleton. Finally, individual FA data were projected onto group skeleton.

DTI-based voxel-wise statistics on the FA maps were carried out using a permutation testing for nonparametric statistics using a GLM design. In a first GLM, we included the three main groups (CTR, AD, and FTD), and we tested for differences between the three groups using age as a covariate. In a second set of analyses, we included individual biomarker values for each group, and subjects' age. We tested for correlations between FA and each biomarker in the three groups, using age as a covariate. This procedure was performed separately for NFL, T-tau, A β , Ng, and 14-3-3.

2.8 | Disease-specific signatures and multiple regression approaches

We created diseases signature maps, obtained from the group comparison analyses, namely CTh_{AD} and CTh_{FTD} and FA_{AD} and FA_{FTD}, for

the CTh and FA maps. In order to obtain descriptive overall patterns of atrophy we first compared FTLT and AD groups separately against the CTR. With the aim to explore differential alterations between FTLT and AD, we created the neuroimaging signatures for each disease by directly comparing the two groups (i.e., AD < FTLT and the FTLT < AD contrasts $p < .05$ corrected) for FA and CTh maps.

After creating these disease-specific signature maps, we obtained individual CTh and FA values for each signature across the entire sample of subjects. We tested multiple regression models in order to evaluate the predictive capabilities of the different biomarkers for each signature, using Akaike Information Criterion (AIC) stepwise algorithm in R (Sakamoto, Ishiguro, & Kitagawa, 1986). For that, we used a sample of $N = 75$ subjects, corresponding to those that had complete sets of MRI and CSF measures. Before multiple regression models, we evaluated pair-wise correlations of the different CSF biomarkers. We then created four separate models for predicting CTh_{AD}, CTh_{FTD}, FA_{AD}, and FA_{FTD}, with A β , T-tau, NFL, Ng, 14-3-3 levels and age as predictors. We used 90% confidence intervals obtained with bootstrapping algorithms to study the significance of the models and the relative importance of each predictor. In addition, we evaluated the multiple regression models corresponding to the hippocampal volume and the MMSE results.

3 | RESULTS

3.1 | Sample demographics, clinical data, and biomarkers

Demographic information, MMSE scores, and median levels of the biomarkers are shown in Table 1. In summary, we found a slightly

TABLE 1 Demographics, clinical data, and CSF-biomarker values

	Group medians			Group comparisons		
	CTR	AD	FTLD	CTR vs. AD <i>p</i> value	CTR vs. FTLD <i>p</i> value	AD vs. FTLD <i>p</i> value
Gender (m/f)	14/34	28/36	14/12	.11	.036	.38
AGE median [Q1, Q3] years	55.7 [49.5, 61.1]	56.6 [54.5, 60.5]	60.6 [55.9, 64.7]	.19	.0033	.019
Disease duration (years to LP)	N/A	2.90 [1.61, 3.79]	2.88 [1.90, 3.78]	N/A	N/A	0.77
A β median [Q1, Q3] pg/ml	745.3 [618.6, 929.7]	392 [315.08, 454.6]	764.5 [626.9, 867.5]	1.1*10⁻¹⁴	.97	2.5*10⁻¹¹
P-tau median [Q1, Q3] pg/ml	48.6 [38.8, 57.0]	105.6 [78.8, 140.6]	45.6 [36.7, 58.8]	3.6*10⁻¹⁵	.68	3.7*10⁻¹⁰
T-tau median [Q1, Q3] pg/ml	229.0 [165.5, 260.1]	690.8 [469.3, 1,033.0]	278.3 [211.5, 425.4]	1.4*10⁻¹⁸	.0013	8.4*10⁻⁹
NfL median [Q1, Q3] pg/ml	801.20 [517.2, 919.2]	1955.8 [1,602, 2,281]	4,682.5 [3,315, 6,048]	9.1*10⁻¹⁸	3.8*10⁻¹¹	1.3*10⁻⁹
14-3-3 median [Q1, Q3] AU	2,532.6 [2,178, 2,734]	4,790.0 [3,708, 6,622]	3,942.5 [2,968, 4,783]	4.2*10⁻¹⁰	2.7*10⁻⁵	.013
Ng median [Q1, Q3] pg/ml	161.8 [125.6, 205.6]	246.3 [181.5, 306.8]	136.2 [92.1, 188.3]	4.2*10⁻⁶	.23	2.4*10⁻⁵
MMSE score median [Q1, Q3]	29.0 [29.0, 30.0]	23.0 [19.0, 26.5]	26.0 [24.0, 27.0]	1*10⁻¹³	5.1*10⁻⁵	.53

Note: Group summaries given as the median and the interquartile range of each measure. Pair-wise differences between groups are calculated using chi-square for gender or Kruskal-Wallis tests for the rest of the variables. Significant group-differences are highlighted in bold (Bonferroni-corrected p threshold = .0018).

Abbreviations: 14-3-3, 14-3-3 γ protein; A β , amyloid-beta protein 42; AD, Alzheimer's disease; AU, arbitrary units; CTR, controls; FTLT, frontotemporal dementia; LP, lumbar puncture; MMSE, mini mental state examination; N/A, not-applicable; NfL, neurofilament light chain; Ng, neurogranine; P-tau, phosphorylated-tau, T-tau, total-tau.

greater proportion of females in the CTR group compared with the FTLD group. FTLD subjects were slightly older than CTR and AD groups ($p < .05$). MMSE scores were lower in both AD and FTLD groups compared with CTR ($p < .05$), but did not differ between AD and FTLD. We found lower $A\beta_{42}$ and higher T-tau and P-tau concentrations in AD compared to FTLD and CTR. Compared to CTR, NfL, and 14-3-3 were higher in both AD and FTD, but in AD and FTLD comparison, NfL were higher in FTLD while 14-3-3 concentration was higher in AD. Ng levels in AD were higher than in CTR and FTLD (Table 1). Furthermore, we sub-analyzed the FTLD group compared to the other types (Table S1). We found significant correlation between several pairs of biomarkers, both in the whole sample or in the different clinical groups (Tables S2–S5).

3.2 | CTh results

3.2.1 | Group differences in CTh

We found reduced CTh in frontal and temporal areas in FTLD compared with CTR, and widespread CTh loss in AD (Figure 1). We use the map resulting from the AD < FTLD contrast to represent the CTh_{AD} signature, and the reverse contrast for the CTh_{FTLD} (see Figure 2a).

3.2.2 | Correlations between CTh and CSF biomarkers

In FTLD, NfL levels showed a significant negative correlation with CTh in a cluster located on the left hemisphere (cluster size = 15,667.98 mm², cluster $p = .0001$), covering mainly frontal areas, including the pars opercularis, the pars triangularis, the middle and superior frontal, and the

precentral (Figure 3) gyrus. We also found a negative correlation between CTh and T-tau levels across several bilateral frontal areas, mainly the superior frontal gyrus (Figure 3). In AD, no correlations were found between biomarker values and CTh.

3.3 | Hippocampal volumes

3.3.1 | Differences across diseases and correlations with biomarkers

We found reduced normalized hippocampal volume in AD and in FTLD compared with CTR ($p = 7.54 \cdot 10^{-10}$ and $p = 4.51 \cdot 10^{-09}$, respectively). No differences in hippocampal volume were found between AD and FTLD ($p = .15$).

When the three clinical groups were pulled together, normalized hippocampal volume showed correlations with $A\beta_{42}$ ($p = .01$, $r = .22$ age-corrected), T-tau ($p = .046$; $r = -.17$), NfL ($p = .01$, $r = -.23$), and Ng ($p = .046$, $r = -.20$). We did not find any significant correlation between normalized hippocampal volumes and CSF biomarkers, when AD, FTLD, and CTR groups were studied separately (all $p > .05$).

3.4 | DTI results

3.4.1 | Group differences in FA

DTI analyses were performed with 112 subjects (49 AD, 23 FTLD, and 40 CTR) with available DTI data of good quality. When comparing FA maps across groups, we found patterns of significantly reduced FA both for AD and FTLD versus CTR. These decreases were found generally across the entire skeleton for both diseases, with predominance

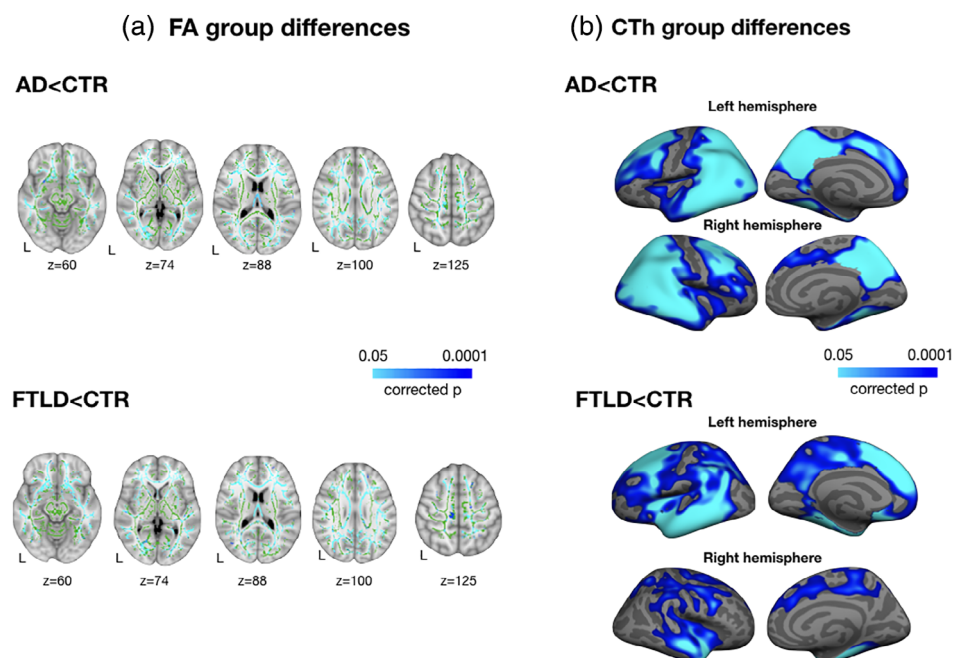
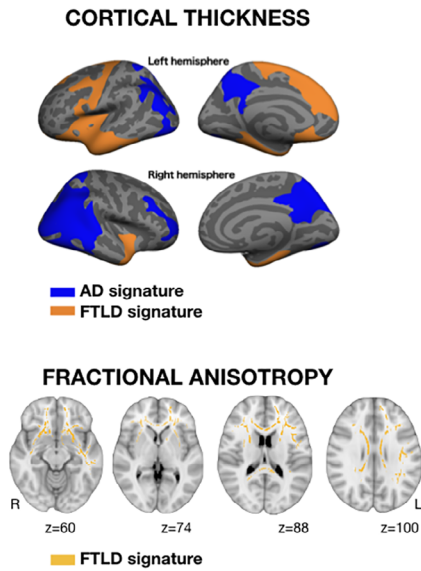


FIGURE 1 Group maps of Alzheimer's disease and frontotemporal lobar degeneration patients compared with CTR. (a) Voxel-wise maps of fraction anisotropy differences, showing only significant regions (corrected $p < .05$) on the standard MNI template. (b) Vertex-wise maps, showing differences in cortical thickness represented on the cortical surface (corrected $p < .05$)

(a) Disease-specific signatures



(b) Relative importance of biomarkers

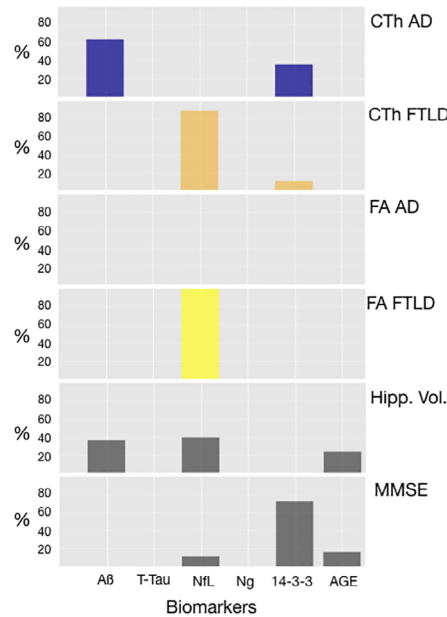


FIGURE 2 (a) Patterns of structural alterations associated with Alzheimer's disease and Frontotemporal Dementia (frontotemporal lobar degeneration, FTLD) (disease signatures). (b) Relative importance (%) of each cerebrospinal fluid biomarker and age in each multiple regression model

in frontal areas and the left hemisphere in FTLD. When the two disease groups were compared, we found greater alterations in the left hemisphere in FTLD, whereas we could not detect areas with lower FA in AD. The signature pattern for FA_{FTLD} was defined as the difference between the $AD > FTLD$ (FA_{FTLD}) maps, cut at $p < .05$ corrected (Figure 2a). The FA_{AD} signature could not be defined due to the lack of significant differences in the $AD > FTLD$ contrast.

3.4.2 | FA and CSF biomarkers correlation analysis

In AD patients, we found a significant negative correlation between NfL values and FA in the forceps minor, the anterior thalamic radiation, the cingulum, the corticospinal tract, the uncinate fasciculus, the inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus, and the temporal part of the superior longitudinal fasciculus. In FTLD patients, FA values in the forceps minor, the anterior thalamic radiation, cingulum, forceps minor, and the left superior longitudinal fasciculus correlated negatively with NfL (Figure 4). T-tau and 14-3-3 showed a negative correlation with FA in the forceps minor for the FTLD group. The remaining biomarkers ($A\beta$, Ng) did not yield any significant results.

3.4.3 | Disease signatures and multiple regression results

The areas within each signature, representing different patterns of structural damage in AD and FTLD, are described previously and shown in Figure 2a.

In the multiple regression analysis, we found that $A\beta_{42}$ and 14-3-3 levels contributed to predict CTh levels within the CTh_{AD} area,

Correlations between CTh and CSF-Biomarkers

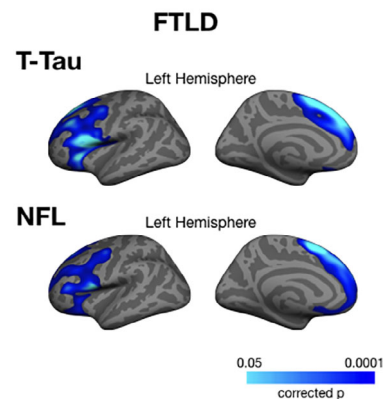


FIGURE 3 Vertex-wise maps of correlations between CTh and cerebrospinal fluid-biomarkers in frontotemporal lobar degeneration subjects

explaining 28% of its variance, whereas CTh values within the CTh_{FTLD} area was better predicted by NfL and 14-3-3, explaining 29% of the variance. For FA values in FA_{FTLD} , NfL was the main predictor, explaining 56% of the variance. No regression analysis was performed for FA values in AD because any regions survived the statistical threshold in $AD > FTLD$ contrast. Ng levels were not predictive in any of the models (Table 2).

In addition to the disease signature patterns, we created models for the hippocampus volumes (using the normalized bilateral volume) and for the MMSE scores. We found that $A\beta_{42}$, NfL, and AGE were the factors that better explained the hippocampal volume (28% of variance), whereas NfL, 14-3-3, and age, predicted the MMSE score (28% variance) through the entire sample.

FIGURE 4 Voxel-wise maps of correlation between fraction anisotropy and cerebrospinal fluid-biomarkers, studied separately for each group

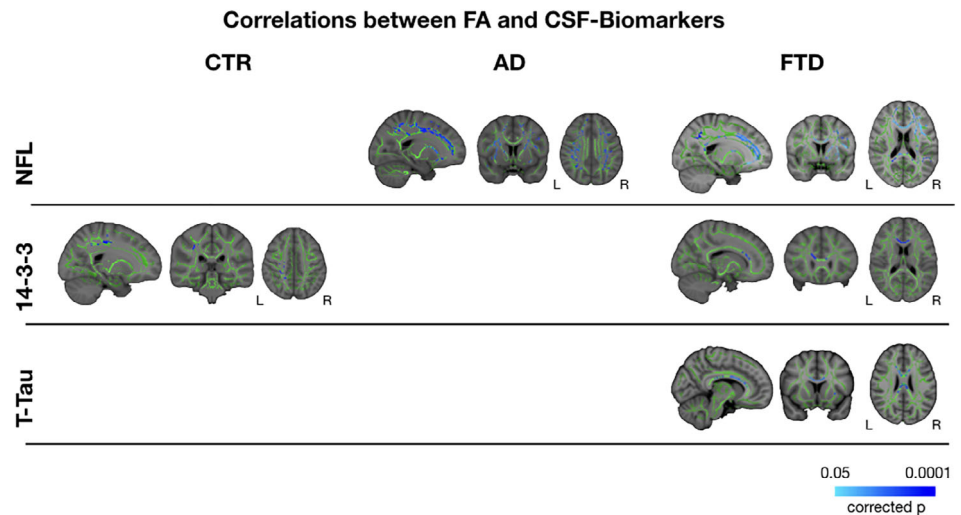


TABLE 2 Contribution of the different biomarkers and AGE to Alzheimer's disease and frontotemporal dementia imaging signatures and to Hippocampal volume and MMSE scores

	A β	T-tau	Nfl	Ng	14-3-3	AGE	R2	Variance explained by model
CTh _{AD}	0.639 [0.19, 0.97]				0.361 [0.033, 0.807]		0.28	28%
FA _{AD}	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CTh _{FTLD}			0.890 [0.52, 0.99]		0.110 [0.001, 0.48]		0.31	29%
FA _{FTLD}			1				0.56	56%
HV	0.365 [0.05, 0.69]		0.398 [0.039, 0.865]			0.237 [0.004, 0.64]	0.28	28%
MMSE			0.117 [0.0004, 0.58]		0.723 [0.22, 0.95]	0.160 [0.012, 0.41]	0.28	28%

Note: These data show results of a multiple regression models. Coefficients are normalized to show relative contribution of each variable.

Abbreviations: 14-3-3, 14-3-3 protein; A β , amyloid-beta protein 42; CTh_{AD}/CTh_{FTLD}, mean cortical thickness values within the AD/FTD signatures; FA_{AD}/FA_{FTLD}, mean FA values within the defined FA/AD signatures. HV, hippocampal volume; MMSE, mini mental state examination; N/A, not applicable; Nfl, neurofilament light chain; Ng, neurogranine; P-tau, phosphorylated-tau, T-tau, total-tau.

For each model, we calculated the relative importance of each predictor and we found that Nfl had the highest impact in CTh_{FTLD} (89%) and it was the only variable depicted for FA_{FTLD}, whereas A β had the highest importance for CTh_{AD} (64%). The most important predictors for the hippocampal volume and for MMSE were Nfl and 14-3-3, respectively (Figure 2b).

4 | DISCUSSION

We performed a cross-sectional study of structural GM and WM alterations and their relationship with CSF biomarkers in early-onset AD and FTLT. Differential patterns of brain loss and CSF biomarkers profiles were found for both diseases. For the AD signatures, we found that, in addition to A β , 14-3-3 was the only neurodegeneration marker that significantly contributed to CTh levels variation, whereas T-tau contributed to FA levels. For FTLT signatures, Nfl and 14-3-3 were the main contributors to both CTh and FA values.

In our cohort, as expected, EOAD patients showed lower A β and higher T-tau and P-tau CSF concentrations compared to FTLT and controls (Mattson, 2017). Nfl concentrations were higher in

both diseases compared with CTR, and in FTLT compared to AD, in concordance with previous publications (Ljubenkov et al., 2018; McFerrin et al., 2017; Sjögren et al., 2000). Ng in AD were higher than controls and FTLT, but not significant differences were found in FTLT with respect to CTR (Gaetani et al., 2019; Wellington et al., 2016; Portelius et al., 2018; Lista, Toschi, Baldacci, et al., 2017). There are few data about 14-3-3 levels in nonprion neurodegenerative disorders, in our cohort, 14-3-3 levels were increased in AD and FTLT compared with CTR and in AD compared with FTLT (Burkhard et al., 2001).

We found cortical and subcortical (hippocampus) GM loss in both AD and FTLT compared with controls. In general, the atrophy pattern was more widespread in AD and presented a fronto-temporal predominance in FTLT in line with previous publications (Möller et al., 2015; Rabinovici et al., 2007). We also found WM integrity loss in both diseases, greater in FTLT than AD. These findings are similar to previous studies evaluating the structural connectivity in neurodegenerative dementias that have suggested more WM damage in FTLT compared to AD, especially in frontal and temporal regions (Canu et al., 2017; Möller et al., 2015; Ossenkoppele et al., 2015; Zhang, Schuff, Du, et al., 2009).

In the multivariate analysis, we found that AD and FTLD neuroimaging signatures were differentially influenced by CSF biomarkers. For AD, $A\beta$ was the biomarker that most contributed to CTh values in AD signature. Unexpectedly 14-3-3 resulted a significant predictor of CTh values while other neurodegeneration markers as T-tau, NfL, and Ng did not. Previous studies have analyzed the contribution of $A\beta$ and T-tau to structural changes in AD (Blennow et al., 2019; Li et al., 2014; Tosun, Schuff, Shaw, et al., 2011). The relevant contribution of $A\beta$ in the CTh AD signature in the present study is plausible given its main role in AD pathophysiology. A plateau effect of the $A\beta$ load in symptomatic stages of the disease has been defined, suggesting that brain atrophy might be more related to tau spread rather than amyloid burden (Blennow & Zetterberg, 2018). In contrast, our results indicate that $A\beta$ levels contribute to the typical AD structural changes observed. Even if this effect might be driven by the fact that low $A\beta$ levels are a hallmark to all the AD subjects included, we believe that it might also suggest an effect in early symptomatic stages. However, we cannot claim that the correlation found between $A\beta$ and cortical brain atrophy in our cohort demonstrates a causal relationship between them. Overall, this finding highlights the complex relationships among different biomarkers through the AD pathology. Moreover, in our cohort, 14-3-3 levels showed a strong correlation with T-tau levels both in the whole group and in the different clinical subgroups. This could suggest that the effect of T-tau observed in other studies could be related to the 14-3-3 effect we observed in this study, while here the strong correlation observed could cancel the effect of T-tau in the regression model. Unfortunately, we could not study the FA_{AD} signature because we did not find any brain area in which FA was significantly different in AD compared with FTLD. This finding is in agreement with previously published data and it could be attributed to a more intense WM damage in FTLD (Möller et al., 2015).

Both CTh and FA values within the FTLD signature were mostly explained by NfL levels, although 14-3-3 levels also contributed. NfL values were associated CTh and FA values in the left frontal and temporal regions in FTLD. These data support that NfL is a neurodegeneration marker strongly related to FTLD (Ljubenkov et al., 2018). These findings are also consistent with previous studies in FTLD patients that reported correlations between brain structure and NfL concentration especially in frontotemporal areas, with predominance in the left hemisphere (Rohrer et al., 2016; Scherling et al., 2014). The relation of NfL with WM changes, beyond the GM loss, is plausible as NfL is an axonal protein (Ossenkopppele et al., 2015). Although we believe that studying the differences through the FTLD spectrum could be of interest, in the present study, the sample was not big enough to perform this approach for the different clinical variants separately.

14-3-3 was also the main factor in MMSE, supporting a role as a nondisease specific marker of neurodegeneration. Regarding hippocampal volume, we found that $A\beta$ and NfL accounted almost equally models suggesting both CSF biomarkers could contribute to the subcortical atrophy, as suggested previously (Idland et al., 2017).

Ng was the only CSF biomarker that did not influence any model, despite being altered in AD subjects even if has been suggested to be a specific biomarker of AD. Although our data further support previously reported elevated CSF Ng concentrations in AD compared with FTLD and controls, it did not reach relevance enough to outstand in the AD statistical model. These results are in line with a recent publication that reported that Ng did not show a diagnostic added value to the classic basic AD biomarkers in terms of diagnostic accuracy (Lista et al., 2017).

We should acknowledge several limitations in this study. First, the relatively small sample size, especially in the FTLD group. In this sense, the inclusion of different clinical FTLD variants can lead to some variability within the FTLD group, but which in turn reflects the heterogeneity of the FTLD itself. We also acknowledge that the fact that the maps obtained from the groups are then used in the analysis with biomarkers that also differ between groups could introduce some circularity. However, we think that the goal of evaluating which biomarkers better explained these structural changes is valid as we use multiple regression models and the relevance of the result is the magnitude of the effect of AD core biomarkers compared to other biomarkers. Further studies in larger cohorts are needed to confirm and expand these data.

In conclusion, our study suggests that biochemical markers might contribute differently to structural (CTh and FA) changes typical of AD and these results support the complexity of the relationship between CSF biomarker and structural brain changes in these diseases.

ACKNOWLEDGMENTS

The authors thank patients, their relatives, and healthy controls for their participation in the research. This work was supported by Spanish Ministry of Economy and Competitiveness-Instituto de Salud Carlos III and Fondo Europeo de Desarrollo Regional (FEDER), Unión Europea, "Una manera de hacer Europa" [PI14/00282 to Dr. A. Lladó], PERIS 2016–2020 Departament de Salut de la Generalitat de Catalunya [SLT002/16/00408 to Dr. Sanchez-Valle] and Fundació Marató de TV3, Barcelona, Spain [Grant 20143810 to Dr. Sanchez-Valle] and CERCA Programme/Generalitat de Catalunya. Dr. Neus Falgàs received funding from Hospital Clinic Barcelona [Ajut Josep Font]. Dr. Anna Antonell (PERIS 2016–2020 SLT002/16/00329) and Dr. Albert Lladó (PERIS SLT008/18/00061) received funding from Departament de Salut de la Generalitat de Catalunya. Dr. Sergi Borrego-Écija is a recipient of a Rio Hortega grant and Dr. Oscar Ramos of a PFIS grant, from the ISCIII, Spain. H.Z. is a Wallenberg Academy Fellow supported by grants from the Swedish Research Council (#2018-02532), the European Research Council (#681712), Swedish State Support for Clinical Research (#ALFGBG-720931) and the UK Dementia Research Institute at UCL. K.B. holds the Torsten Söderberg Professorship in Medicine at the Royal Swedish Academy of Sciences, and is supported by the Swedish Research Council (#2017-00915), the Swedish Alzheimer Foundation (#AF-742881), Hjärtfonden, Sweden (#FO2017-0243), and a grant (#ALFGBG-715986) from the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement.

CONFLICT OF INTEREST

H.Z. has served at scientific advisory boards of Roche Diagnostics, Wave, Samumed and CogRx, has given lectures in symposia sponsored by Biogen and Alzecure, and is a cofounder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg (all outside the submitted work). K.B. has served as a consultant or at advisory boards for Alector, Biogen, CogRx, Lilly, MagQu, Novartis, and Roche Diagnostics, and is a cofounder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg, all unrelated to the work presented in this article. The other authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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How to cite this article: Falgàs N, Ruiz-Peris M, Pérez-Millan A, et al. Contribution of CSF biomarkers to early-onset Alzheimer's disease and frontotemporal dementia neuroimaging signatures. *Hum Brain Mapp*. 2020;1–10. <https://doi.org/10.1002/hbm.24925>