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Cerebrospinal Fluid and Plasma Biomarkers do not Differ in the Presenile and Late-Onset Behavioral Variants of Frontotemporal Dementia

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Abstract.

Background: Memory troubles and hippocampal atrophy are considered more frequent and focal atrophy less severe in late-onset (>65 years) than in presenile behavioral variant frontotemporal dementia (bvFTD).

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Objective: To compare cerebrospinal fluid (CSF) and plasma biomarkers in late-onset and presenile bvFTD.

Methods: Multicentric retrospective study (2007-2017) on patients with clinical diagnosis of bvFTD.

Results: This study included 44 patients (67%) with presenile and 22 (33%) with late-onset bvFTD (comparable mean disease duration; $n = 11$ with causal mutations). Hippocampal atrophy was more frequent (80% versus 25.8%) and severe in late-onset bvFTD (median Scheltens score: 3 [0–4] versus 1 [0–3]), without difference after adjustment for age. Lobar atrophy and focal hypometabolism/hypoperfusion were not different between groups. The median CSF $A\beta_{1-42}$ and phosphorylated tau (P-tau) concentrations were in the normal range and comparable between groups. Axonal neurodegeneration biomarkers were within the normal range (CSF T-tau; plasma T-tau in late-onset bvFTD) or higher (plasma neurofilament light chain (NFL); plasma T-tau in presenile bvFTD) than the normal values, but globally not different between bvFTD groups. Plasma glial fibrillary acid protein (GFAP) was strongly increased in both bvFTD groups compared with the values in controls of the same age.

Conclusion: The CSF and plasma biomarker profiles did not suggest a more aggressive neurodegeneration in the presenile group (comparable T-tau, NFL, and GFAP levels) or the co-existence of Alzheimer's disease in the late-onset group (comparable and within normal range CSF $A\beta_{1-42}$ and P-tau). The severity of the neurodegenerative process seems comparable in presenile and late-onset bvFTD.

Keywords: Biomarkers, cerebrospinal fluid, frontotemporal dementia, glial fibrillary acid protein, late-onset, neurofilament light chain

INTRODUCTION

The *in vivo* diagnosis of the behavioral variant of frontotemporal dementia (bvFTD) is based on clinical and radiological features [1]. Age at onset is usually younger than 65 years, but late-onset (after 65 years of age) bvFTD is not rare and could represent up to 40% of all bvFTD cases [2, 3]. Late-onset bvFTD is characterized by more severe memory loss and hippocampal atrophy, and less frontal and temporal lobe atrophy compared with the classical presenile bvFTD [2, 4, 5, 6, 7]; however, some studies suggested no difference between early-onset and late-onset bvFTD in terms of neuropsychological evaluation and functional outcomes [3]. These clinical and radiological differences might be due to a more aggressive disease in presenile onset bvFTD, suggested by exacerbated focal atrophy, and/or to co-existent amyloid- β ($A\beta$) deposits in late-onset bvFTD, suggested by more frequent episodic memory alteration and hippocampal atrophy.

Cerebrospinal fluid (CSF) and plasma biomarkers had never been compared in presenile and late-onset bvFTD. In frontotemporal dementia, biomarkers of axonal damage, such as tau and neurofilament light chain (NFL), are associated with poor survival, active disease, and conversion from pre-symptomatic to symptomatic stages [8, 9, 10]. In case of co-existing Alzheimer's disease (AD) pathology, biomarkers analysis should show a decreased $A\beta_{1-42}$ and an increased phosphorylated P-tau (P-tau) (two markers of AD pathology) in the late-onset bvFTD group.

Therefore, in this study, we wanted to precisely determine the clinical, radiological, and biological features (particularly CSF and plasma biomarkers) of presenile and late-onset bvFTD.

METHODS

Study sample

This retrospective (2007–2017) multicentric (Montpellier, Paris, and Besancon Clinical Memory Centers) study included all patients with a possible, probable, or definite diagnosis of bvFTD [1] with available clinical data and CSF samples. Patients were then classified as having presenile or late-onset bvFTD in function of their age at disease onset (\leq and >65 years of age, respectively).

All patients signed a written informed consent approved by the Local Ethics Committee (registered DC-2008-417). To limit possible confounding factors and misdiagnosis, patients with psychiatric conditions that could explain the cognitive and behavioral alterations or with radiological evidence of severe vascular burden (Fazekas scale score ≥ 3 on brain magnetic resonance imaging (MRI), or severe vascular leucoencephalopathy on brain computed tomography (CT)) [11, 12] were excluded.

Laboratory, neuropsychological, and neuroimaging data at the initial evaluation were retrospectively collected; as lumbar puncture is generally part of the initial work-up of patients with possible bvFTD, the day of lumbar puncture was considered as the

reference time for the initial evaluation. All clinical, neuropsychological, and radiological evaluations were performed on the same day or within 6 months after lumbar puncture; plasma and CSF samples were collected on the same day.

The presence of memory or cognitive symptoms and of psychiatric, behavioral, and language problems was evaluated using the patients' clinical notes, reviewed by one of the authors (CM). Hippocampal memory dysfunction was objectively assessed using the Free and Cued Selective Reminding Test [13]. Clinical parkinsonism was considered as present when signs of extrapyramidal syndrome (bradykinesia, hypokinesia, rigidity, tremor) were clearly mentioned in the clinical notes; the Unified Parkinson's Disease Rating Scale-III score was not available.

Control blood samples for T-Tau, NFL, and glial fibrillary acid protein (GFAP) were from participants in a dementia prevention program who did not show any evidence of cognitive impairment or degenerative process after at least 2 years of follow-up following the first evaluation (including neuropsychological examination, cerebral MRI, and lumbar puncture). Controls were separated in group 1 (N=19; median age at plasma sample: 60 years) and group 2 (N=18, median age at plasma sample: 72 years), matched with the presenile and late-onset bvFTD groups, respectively, on the basis of the median age at plasma sampling.

Biomarker measurements

CSF was collected in polypropylene tubes using a standardized procedure [14]. CSF A β ₁₋₄₂, total tau (T-tau), and P-tau on threonine 181 were simultaneously measured in each sample using the standardized commercial Innostest[®] sandwich ELISA according to the manufacturer's instructions (Fujirebio Ghent Belgium). The Innostest Amyloid Tau Index (IATI) [15], the modified A β ₁₋₄₂/T-tau ratio currently used in clinical practice, was also calculated. The cut-off values were determined according to the study on harmonization of collection tubes for AD diagnosis performed by Lehmann and colleagues (i.e., 700 pg/mL for A β ₁₋₄₂, 400 pg/mL for T-tau, 60 pg/mL for P-tau) [16].

Blood samples were collected in K2-EDTA vacuum tubes on the morning of lumbar puncture day. Tubes were transported at room temperature to the laboratory within 4 h and centrifuged at 2,000 g for 10 min. After centrifugation, each supernatant was

divided in 500 μ L aliquots and stored at -80°C until use. Plasma T-tau, NFL, and GFAP were measured with a commercial multiplex assay from Quanterix, USA (Simoa-HD1). The lower limits of quantification for T-tau, NFL, and GFAP were 0.10 pg/mL, 0.24 pg/mL, and 0.47 pg/mL, respectively. Quality control samples with high and low values were analyzed in triplicate using five consecutive series of kit batch 501715 and four consecutive series of kit batch 501797. Overall, the inter-assay coefficients of variation (CV) for plasma T-tau, NFL, and GFAP were lower than 13%, 12%, and 5% and the intra-assay CV were lower than 6%, 10%, and 4%, respectively.

Control plasma samples were collected following the same procedure and were stored at the Neurocognition Biobank - CHU Montpellier.

Brain MRI data

Brain MRI data were reviewed by a senior neuroradiologist (NMC). The presence of hippocampal atrophy (Scheltens score ≥ 2) [17], global or focal atrophy, parietal atrophy (Koedam score) [18], and vascular white matter hyper-intensities (Fazekas and Schmidt score) were quantified with the indicated scores [11, 12]. The presence of global or frontal atrophy was evaluated visually, without any quantification or volumetric analysis. If brain MRI was not available, brain CT data were used to determine the presence of global or focal atrophy and of vascular hypodensities. Functional studies were performed with technetium-99m hexamethylpropylene amine oxime (99mTc-HMPAO) single-photon emission computed tomography (SPECT) or fluorine-18 fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET) and visually reviewed by a senior nuclear radiologist (DDV) to evaluate the presence of focal frontotemporal hypometabolism or hypoperfusion. As this is a retrospective study, not all participants underwent structural and functional imaging.

Statistical analysis

For descriptive purposes, quantitative variables were expressed as mean and standard deviation (normal distribution) or as median, minimum, and maximum (non-normal distribution). Qualitative variables were expressed as percentages. Clinical, biological, and neuroradiological characteristics were compared between groups (presenile versus late-onset bvFTD) using multivariate logistic

189 regression models adjusted for age at lumbar
190 puncture. For quantitative variables, linearity was
191 assessed. Age at disease onset was compared with
192 the Mann-Whitney test because the logistic model
193 did not converge due to complete separation of data
194 distribution. Statistical analyses were performed with
195 the SAS software, version 9.4 (SAS Institute).

196 RESULTS

197 Study population

198 This study included 66 patients with a clinical diag-
199 nosis of bvFTD [1] (Table 1) among whom 44 (67%)
200 had the early onset (presenile bvFTD) and 22 (33%)
201 the late onset form (late-onset bvFTD). The diagnosis
202 was possible bvFTD in 14 (21%; $n = 8$ in the prese-
203 nile bvFTD and $n = 6$ in the late-onset bvFTD group),
204 probable bvFTD in 41 (67%; $n = 27$ in the presenile
205 bvFTD and $n = 14$ in the late-onset bvFTD group),
and definite bvFTD with confirmed genetic mutation

206 in 11 patients (17%; $n = 9$ in the presenile bvFTD
207 and $n = 2$ in the late-onset bvFTD group). The dis-
208 tribution of possible, probable, and definite bvFTD
209 diagnoses was comparable between groups (Table 1;
210 $p = 0.44$). The diagnosis of definite bvFTD tended to
211 be more frequent, although not significantly, in the
212 presenile bvFTD than in the late-onset bvFTD group
213 (20.5%, $n = 9$ versus 9%, $n = 2$; $p = 0.2$). Mutations
214 in the *C9ORF72* gene were found in 10 patients,
215 and a mutation in *GRN* (granulin) in one patient; no
216 patient carried mutations in the *MAPT* (microtubule
217 associated protein tau) gene (data not shown).

218 The median age at disease onset was 59 [39–65]
219 years in the presenile bvFTD and 69 [66–77] years in
220 late-onset bvFTD group. The median age at lumbar
221 puncture was significantly younger in the presenile
222 than late-onset bvFTD group (62 [41–69] years ver-
223 sus 71.5 [66–80] years; $p = 0.004$). Sex distribution
224 (59% versus 54.55% of men, $p = 0.72$), disease dura-
225 tion at lumbar puncture (median = 3 [0–19] versus 2
226 [0–10] years; $p = 0.28$), and total follow-up duration
227 (median = 5 [1–19] versus 3 [1–12] years; $p = 0.23$)

Table 1
Demographic and clinical features

Variables	Presenile bvFTD (onset ≤ 65 years) (N = 44, 67%)	Late-onset bvFTD (onset > 65 years) (N = 22, 33%)	Crude model p	Model adjusted for age at lumbar puncture p
<i>Diagnosis confidence level</i>				
– Possible bvFTD, N (%)	8 (18.2%)	6 (27.3%)	0.44	0.40
– Probable bvFTD, N (%)	27 (61.4%)	14 (63.6%)		
– Definite bvFTD, N (%)	9 (20.5%)	2 (9.1%)		
Sex: M	26 (59.1%)	12 (54.6%)	0.72	0.18
Age at onset (y), median [min–max]	59 [39–65]	69 [66–77]	* <0.0001	NA
Age at lumbar puncture day (y), median [min–max]	62 [41–69]	71.5 [66–80]	0.004	NA
Disease duration at lumbar puncture day (y), median [min–max]	3 [0–19]	2 [0–10]	0.28	0.11
Total follow-up (y), median [min–max]	5 [1–19]	3 [1–12]	0.23	0.07
<i>First symptoms (each patient could have one or more symptoms)</i>				
– Memory deficit, N (%)	12 (27.3%)	11 (50%)	0.07	0.75
– Cognition deficit, other, N (%)	3 (6.8%)	2 (9.1%)	0.74	0.30
– Behavior alterations, N (%)	26 (59.1%)	10 (45.5%)	0.29	0.27
– Psychiatric troubles, N (%)	13 (29.5%)	3 (13.6%)	0.17	0.80
– Language difficulties, N (%)	3 (6.8%)	5 (22.7%)	0.08	0.18
<i>Neuropsychological evaluation</i>				
Hippocampal memory dysfunction (Free and Cued Selective Reminding Test), N (%)	11 (27.5%)	11 (50%)	0.08	0.94
Clinical parkinsonism, N (%)	8 (18.2%)	10 (45.4%)	0.02	0.28
Mattis DSR, mean (std)	118 (19)	116 (14)	0.74	0.32
MMSE, median [min–max]	25 [3–30]	20 [14–27]	0.37	0.29
<i>Cognitive and behavioral symptoms</i>				
– Perseverations/Stereotyped behavior, N (%)	34 (89.5%)	12 (80%)	0.37	0.36
– Apathy, N (%)	30 (73.2%)	16 (84.2%)	0.35	0.73
– Hyperorality, N (%)	17 (54.8%)	4 (36.4%)	0.30	0.48
– Executive dysfunction relatively sparing memory, N (%)	37 (92.5%)	18 (81.8%)	0.22	0.74
– Indifference, N (%)	28 (80%)	13 (86.7%)	0.58	0.94
– Disinhibited /Aggressive behavior, N (%)	31 (86.1%)	13 (81.2%)	0.65	0.36

bvFTD, behavioral variant of frontotemporal dementia; DSR, Dementia Rating Scale; MMSE, Mini-Mental State Examination; std, standard deviation. *Mann-Whitney test.

were comparable between groups (presenile versus late-onset bvFTD) (Table 1).

Concerning the initial clinical presentation (Table 1), the percentage of patients with memory or cognitive troubles, and with psychiatric, behavioral, or language problems was not significantly different between groups. Memory complaints (50% versus 27.3%; $p=0.07$) and hippocampal memory dysfunction (50% versus 27.5%; $p=0.08$) tended to be more frequent (not significant) in the late-onset than presenile bvFTD group. The Mini-Mental State Examination (MMSE) (25 [3–30] versus 20 [14–27], $p=0.74$) and Mattis Dementia Rating Scale (Mattis DRS) (118 ± 19 versus 116 ± 14 , $p=0.58$) median and mean scores, respectively, at lumbar puncture were not significantly different between patients with presenile and late-onset bvFTD (Table 1).

Brain imaging data

Cerebral MRI was performed in 47 patients and CT in 10. 99mTc-HMPAO-SPECT or ^{18}F -FDG-PET data were available for 48 patients (73%). A DaTSCAN study to assess dopamine deficiency was available for 19 patients (29%).

Clinical parkinsonism was more frequent in the late-onset bvFTD group (45.4%) than in the presenile bvFTD group (18.2%; $p=0.02$) and pathological DaTSCAN results tended to be more frequent in the late-onset bvFTD group (83.3% versus 30.8%; $p=0.05$) (Tables 1 and 2). These differences were no longer significant after adjustment for age.

Lobar frontotemporal atrophy was detected only in 53% of patients and the frequency was not different between groups (59% versus 47.1%; $p=0.41$). Frontotemporal hypometabolism (^{18}F -FDG-PET) or hypoperfusion (99mTc-HMPAO-SPECT) was detected in 79.5% of patients, but without difference

between groups (78.1% versus 81.2% of patients with presenile bvFTD and late-onset bvFTD, respectively; $p=0.80$) (Table 2).

Conversely, hippocampal atrophy (i.e., mean Scheltens score ≥ 2) was more frequent in the late-onset bvFTD group (80% versus 25.8%; crude model $p=0.001$), and the median of the mean Scheltens score [(Right Scheltens + Left Scheltens)/2] was higher in the late-onset than in the presenile bvFTD group (3 [0–4] versus 1 [0–3]; crude model $p=0.001$) (Table 2). These differences were not significant after adjustment for age.

Plasma and CSF biomarkers

CSF analysis showed that the mean $\text{A}\beta_{1-42}$, T-tau, P-tau, and IATI values were within the normal limits and without significant differences between bvFTD groups (Table 3). According to the A/T/N descriptive classification [19], no patient with bvFTD had a CSF profile highly suggestive of AD pathophysiological process (i.e., A+/T+/N+ = low $\text{A}\beta_{1-42}$ /high P-tau/high T-tau levels). However, 22 patients (33%) presented some abnormalities in CSF biomarkers. Specifically, isolated low $\text{A}\beta_{1-42}$ (A+/T-/N- profile) was detected in four patients with presenile bvFTD and in three with late-onset bvFTD. $\text{A}\beta_{1-42}$ was decreased and T-tau was increased (A+/T-/N+ profile) in one patient with definite diagnosis of late bvFTD due to a *C9ORF72* mutation. T-tau and P-tau (A-/T+/N+ profile) were increased in one patient with presenile bvFTD and in three with late-onset bvFTD (one with definite diagnosis of late-onset bvFTD due to a *C9ORF72* mutation). P-tau was increased (A-/T+/N- profile) in four patients with presenile bvFTD, and T-tau was increased (A-/T-/N+ profile) in two patients with late-onset bvFTD and in four patients with presenile bvFTD

Table 2
Imaging data

Variables	Presenile bvFTD (onset ≤ 65 years)	Late-onset bvFTD (onset > 65 years)	Crude model p	Model adjusted for age at lumbar puncture p
Hippocampal atrophy (MRI), n (%)	8 (25.8%)	12 (80%)	0.001	0.10
Mean Scheltens score = (Right + Left)/2, median [min–max]	1 [0–3]	3 [0–4]	0.001	0.16
Lobar frontotemporal atrophy (MRI), N (%)	23 (59%)	8 (47.1%)	0.41	0.21
Pathological DaTSCAN, N (%)	4 (30.8%)	5 (83.3%)	0.05	0.72
Frontotemporal hypometabolism/perfusion (^{18}F FDG-PET/99mTc-HMPAO-SPECT), N (%)	25 (78.1%)	13 (81.2%)	0.8	0.18

bvFTD, behavioral variant of frontotemporal dementia; ^{18}F FDG-PET, Fluorine-18 Fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; std, standard deviation; 99mTc-HMPAO-SPECT, technetium-99 m hexamethylpropylene amine oxime single photon emission computed tomography.

(two with definite presenile bvFTD due to *GRN* and *C9ORF72* mutations) (data not shown).

The results of T-tau, NFL, and GFAP quantification in plasma samples were available for 26 patients (39%; 14 in the presenile and 12 in the late-onset bvFTD group).

Plasma NFL and GFAP concentrations increased with age, and were significantly higher in patients with presenile and late-onset bvFTD than in healthy controls with matched median age at blood sampling (Table 4). Compared with healthy controls, plasma T-tau concentration was higher in the presenile bvFTD but not in the late-onset bvFTD group (Table 4). No significant difference was found in plasma NFL, GFAP, and T-tau concentration between bvFTD groups (Table 3).

DISCUSSION

Here, we presented and compared clinical, radiological, and biological data of patients with presenile and late-onset bvFTD, by focusing particularly on CSF and plasma biomarkers. For the definition of presenile and late-onset bvFTD, we chose an age cut-off of 65 years, in agreement with most literature data [4]. BvFTD is a rare disease, and the late-onset variant is even rarer. Therefore, a strength of our study is the inclusion of clinically well-characterized patients and the measurements of CSF and plasma biomarkers in most of them. We confirmed that hippocampal atrophy is more frequent in the late-onset group and also found a tendency towards more episodic memory alterations in this group of patients. The other clinical and radiological parameters were not different between groups. Previous anatomopathological series [4] reported comparable frequency of frontal and temporal atrophy in patients with presenile and late-onset bvFTD, although atrophy was more severe in the presenile group. In our series, ^{18}F -FDG-PET and $^{99\text{mTc}}$ -HMPAO- SPECT were more sensitive than cerebral MRI in detecting cortical focal involvement, without differences between presenile and late-onset bvFTD; however, these techniques did not allow quantifying and comparing the cortical atrophy severity in the two groups. Moreover, the clinical criteria used for the diagnosis of bvFTD in our study might not have allowed including patients with more atypical late-onset disease [20, 21]. Nevertheless, the percentage of patients with late-onset bvFTD in our series (about 30%) is comparable to what reported in the literature [21].

Comparison of the CSF and plasma biomarkers did not highlight any evidence of more aggressive disease in the presenile or late-onset bvFTD group. Indeed, plasma NFL concentration was comparable between presenile and late-onset patients and was higher than in age-matched controls in both bvFTD groups. Plasma T-tau was higher than in age-matched controls only in the presenile bvFTD group and was not significantly different between bvFTD groups. Conversely, CSF T-tau level was within the normal limit and not different between bvFTD groups. This is different from other neurodegenerative diseases, for instance AD, where CSF T-tau and P-tau levels are much higher in the early-onset form than in the classical late-onset form [22, 23, 24]. Unfortunately, the available data did not allow comparing disease progression in the two bvFTD groups (missing information). Previous anatomopathological studies showed a comparable or slightly shorter disease duration (from onset to death) in patients with late-onset bvFTD compared with those with the presenile variant [4, 5].

The glial marker GFAP was strongly increased in both bvFTD groups compared with controls. Although the number of patients with data on plasma biomarkers was low, these results are in line with some recent studies showing that CSF GFAP concentration is increased in patients with neurodegenerative diseases, particularly FTD. The reasons of the increase of this glial marker remain elusive [25, 26].

The mean values of the CSF biomarkers of AD ($\text{A}\beta_{1-42}$, T-tau, and P-tau) were normal and not different between bvFTD groups, suggesting that the presence of hippocampal atrophy and episodic memory problems might not be explained by co-existent AD. The increased frequency and severity of hippocampal atrophy in the late-onset group could simply be due to age. Indeed, the differences between presenile and late-onset bvFTD were no longer significant after adjustment for age. However, according to our criteria, hippocampal atrophy was considered as present only when severe (Scheltens score ≥ 2), and it does not seem likely that its severity is only age-related [27]. Alternatively, hippocampal atrophy could be part of bvFTD pathological process and linked to hippocampal sclerosis, as suggested also by anatomopathological series showing that hippocampal sclerosis is present in FTD, affects all anatomopathological subtypes, and is significantly more common in late-onset cases [5]. A future study in which patients with bvFTD are compared with age-

Table 3
CSF and plasma biomarkers data

CSF	Presenile bvFTD (onset ≤ 65 years) (N = 44)	Late-onset bvFTD (onset > 65 years) (N = 22)	Crude model <i>p</i>	Model adjusted for age at lumbar puncture
Aβ ₁₋₄₂ (pg/mL) (nv >700 pg/mL), mean (std)	1026.1 (243.1)	995.2 (323.9)	0.66	0.28
T-tau (pg/mL) (nv <400 pg/mL), median [min–max]	252.5 [80–620]	226.33 [104.89–827.56]	0.29	0.30
P-tau (pg/mL) (nv <60 pg/mL), median [min–max]	41 [19–78]	39 [15–88]	0.73	0.44
IATI (nv >0.8), mean (std)	1.9 (0.6)	1.8 (0.7)	0.35	0.31
Plasma (multiplex assay)	Presenile bvFTD (onset ≤ 65 years) (N = 14)	Late onset bvFTD (onset > 65 years) (N = 12)	Crude model <i>p</i>	Model adjusted for age at lumbar puncture
NFL (pg/mL), median [min–max]	24.99 [8.25–112.59]	30.88 [9.76–75.29]	0.87	0.54
Tau (pg/mL), median [min–max]	0.53 [0.31–1.03]	0.38 [0.20–1.27]	0.45	0.31
GFAP (pg/ml), median [min–max]	176.6 [72.4–460.3]	212.27 [86.86–612.77]	0.27	0.24

bvFTD, behavioral variant of frontotemporal dementia; IATI, Innotech Amyloid Tau Index; nv, normal value; std, standard deviation; NFL, neurofilament light chain; GFAP, glial fibrillary acid protein.

Table 4
Plasma NFL, tau, and GFAP in controls and in patients with presenile and late-onset bvFTD

Variable	Controls (N = 19)	Presenile bvFTD (N = 14)	<i>p</i>	Controls (N = 18)	Late-onset bvFTD (N = 12)	<i>p</i>
Age at blood sampling (y), median [min–max]	60 [59–61]	62 [41–69]	0.09	72 [68–73]	71.5 [66–80]	0.9
NFL (pg/mL), median [min–max]	9.36 [5.86–36.83]	24.99 [8.25–112.59]	0.0003	11.1 [6.75–21.03]	30.88 [9.76–75.29]	<0.0001
Tau (pg/mL), median [min–max]	0.39 [0.15–2.45]	0.53 [0.31–1.03]	0.02	0.36 [0.04–0.56]	0.38 [0.2–1.27]	0.23
GFAP (pg/ml), median [min–max]	41.64 [12.14–81.29]	176.6 [72.24–460.3]	<0.0001	72.94 [34.39–121.6]	212.27 [86.86–612.87]	<0.0001

bvFTD, behavioral variant of frontotemporal dementia; std, standard deviation; NFL, neurofilament light chain; GFAP, glial fibrillary acid protein.

matched healthy controls might bring some insights into this issue.

The lack of anatomopathological data, the possible disease heterogeneity, the absence of quantitative assessment of frontotemporal atrophy, and the relatively small number of patients are some limits of this study, and might explain the absence of differences between groups.

In conclusion, our findings might contribute to better understand bvFTD physiopathology and facilitate the diagnosis of late-onset forms. We confirmed that clinical and radiological hippocampal alterations are an important feature of bvFTD, and they might be more frequent in the late-onset form. We cannot rule out a role of aging to explain this finding, whereas we excluded the role of co-existent AD pathology in late-onset bvFTD. Indeed, although the clinical presentation could be confusing, CSF and plasma biomarker quantification should allow the reliable differentiation between late-onset bvFTD and AD [28]. Moreover, unlike T-tau, other biomarkers of neurodegeneration, such as NFL and GFAP, seem to

be increased in bvFTD compared with controls, but without any biological evidence of a more aggressive neurodegeneration in presenile compared with late-onset bvFTD.

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REFERENCES

- [1] Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EGP, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini M-L, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub

- 442 S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt
443 V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman
444 J, Cappa SF, Freedman M, Grossman M, Miller BL (2011)
445 Sensitivity of revised diagnostic criteria for the behavioural
446 variant of frontotemporal dementia. *Brain* **134**, 2456–2477.
- 447 [2] Shinagawa S, Toyota Y, Ishikawa T, Fukuhara R, Hokoishi
448 K, Komori K, Tanimukai S, Ikeda M (2008) Cognitive
449 function and psychiatric symptoms in early- and late-onset
450 frontotemporal dementia. *Dement Geriatr Cogn Disord* **25**,
451 439–444.
- 452 [3] Borroni B, Agosti C, Bellelli G, Padovani A (2008) Is early-
453 onset clinically different from late-onset frontotemporal
454 dementia? *Eur J Neurol* **15**, 1412–1415.
- 455 [4] Baborie A, Griffiths TD, Jaros E, Momeni P, McKeith IG,
456 Burn DJ, Keir G, Larner AJ, Mann DM, Perry R (2012)
457 Frontotemporal dementia in elderly individuals. *Arch Neurol*
458 **69**, 1052–1060.
- 459 [5] Baborie A, Griffiths TD, Jaros E, McKeith IG, Burn DJ,
460 Richardson A, Ferrari R, Moreno J, Momeni P, Duplessis
461 D, Pal P, Rollinson S, Pickering-Brown S, Thompson JC,
462 Neary D, Snowden JS, Perry R, Mann DMA (2011) Patho-
463 logical correlates of frontotemporal lobar degeneration in
464 the elderly. *Acta Neuropathol (Berl)* **121**, 365–371.
- 465 [6] Baborie A, Griffiths TD, Jaros E, Momeni P, McKeith IG,
466 Burn DJ, Keir G, Larner AJ, Mann DM, Perry R (2013)
467 Elderly individuals with FTL D. *JAMA Neurol* **70**, 412–413.
- 468 [7] Ye BS, Choi SH, Han S-H, Kim S, Yang D-W, Park KH, Han
469 HJ, Youn YC, Choi B-O, Kim SH, Woo S-Y, Na DL, Kim
470 E-J (2015) Clinical and neuropsychological comparisons of
471 early-onset versus late-onset frontotemporal dementia: A
472 CREDOS FTD Study. *J Alzheimers Dis* **45**, 599–608.
- 473 [8] Meeter LH, Dopper EG, Jiskoot LC, Sanchez-Valle R, Graff
474 C, Benussi L, Ghidoni R, Pijnenburg YA, Borroni B, Galim-
475 berti D, Laforce RJ, Masellis M, Vandenberghe R, Ber IL,
476 Otto M, van Minkelen R, Pappa JM, Rombouts SA, Bal-
477 asa M, Öijerstedt L, Jelic V, Dick KM, Cash DM, Harding
478 SR, Jorge Cardoso M, Ourselin S, Rossor MN, Padovani A,
479 Scarpini E, Fenoglio C, Tartaglia MC, Lamari F, Barro C,
480 Kuhle J, Rohrer JD, Teunissen CE, van Swieten JC (2016)
481 Neurofilament light chain: A biomarker for genetic fronto-
482 temporal dementia. *Ann Clin Transl Neurol* **3**, 623–636.
- 483 [9] Meeter LHH, Vijverberg EG, Del Campo M, Rozemuller
484 AJM, Donker Kaat L, de Jong FJ, van der Flier WM,
485 Teunissen CE, van Swieten JC, Pijnenburg YAL (2018)
486 Clinical value of neurofilament and phospho-tau/tau ratio
487 in the frontotemporal dementia spectrum. *Neurology* **90**,
488 e1231–e1239.
- 489 [10] Rohrer JD, Woollacott IOC, Dick KM, Brotherhood E,
490 Gordon E, Fellows A, Toombs J, Druey R, Cardoso MJ,
491 Ourselin S, Nicholas JM, Norgren N, Mead S, Andreasson
492 U, Blennow K, Schott JM, Fox NC, Warren JD, Zetterberg H
493 (2016) Serum neurofilament light chain protein is a measure
494 of disease intensity in frontotemporal dementia. *Neurology*
495 **87**, 1329–1336.
- 496 [11] Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman
497 RA (1987) MR signal abnormalities at 1.5 T in Alzheimer's
498 dementia and normal aging. *AJR Am J Roentgenol* **149**,
499 351–356.
- 500 [12] Schmidt R, Fazekas F, Kleinert G, Offenbacher H, Gindl
501 K, Payer F, Freidl W, Niederkorn K, Lechner H (1992)
502 Magnetic resonance imaging signal hyperintensities in the
503 deep and subcortical white matter. A comparative study
504 between stroke patients and normal volunteers. *Arch Neurol*
505 **49**, 825–827.
- [13] Grober E, Buschke H, Crystal H, Bang S, Dresner R (1988) 506
507 Screening for dementia by memory testing. *Neurology* **38**,
508 900–903.
- [14] Teunissen CE, Verwey NA, Kester MI, van Uffelen K,
509 Blankenstein MA (2010) Standardization of assay proce-
510 dures for analysis of the CSF biomarkers amyloid β ((1-42)),
511 tau, and phosphorylated tau in Alzheimer's disease: Report
512 of an international workshop. *Int J Alzheimers Dis* **2010**,
513 635053.
- [15] Hulstaert F, Blennow K, Ivanou A, Schoonderwaldt HC,
514 Riemenschneider M, De Deyn PP, Bancher C, Cras P, Wilt-
515 fang J, Mehta PD, Iqbal K, Pottel H, Vanmechelen E,
516 Vanderstichele H (1999) Improved discrimination of AD
517 patients using beta-amyloid(1-42) and tau levels in CSF.
518 *Neurology* **52**, 1555–1562.
- [16] Lehmann S, Schraen S, Quadrio I, Paquet C, Bombois
519 S, Delaby C, Dorey A, Dumurgier J, Hirtz C, Krolak-
520 Salmon P, Laplanche J-L, Moreaud O, Peoc'h K, Rouaud
521 O, Sablonnière B, Thouvenot E, Touchon J, Vercrusse O,
522 Hugon J, Gabelle A, Pasquier F, Perret-Liaudet A (2014)
523 Impact of harmonization of collection tubes on Alzheimer's
524 disease diagnosis. *Alzheimers Dement* **10**, S390-S394.e2.
525
- [17] Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC,
526 Verwersch P, Kuiper M, Steinling M, Wolters EC, Valk J
527 (1992) Atrophy of medial temporal lobes on MRI in "prob-
528 able" Alzheimer's disease and normal ageing: Diagnostic
529 value and neuropsychological correlates. *J Neurol Neuro-
530 surg Psychiatry* **55**, 967–972.
- [18] Koedam ELGE, Lehmann M, van der Flier WM, Scheltens
531 P, Pijnenburg YAL, Fox N, Barkhof F, Wattjes MP (2011)
532 Visual assessment of posterior atrophy development of a
533 MRI rating scale. *Eur Radiol* **21**, 2618–2625.
- [19] Jack CR, Bennett DA, Blennow K, Carrillo MC, Feldman
534 HH, Frisóni GB, Hampel H, Jagust WJ, Johnson KA, Knop-
535 man DS, Petersen RC, Scheltens P, Sperling RA, Dubois
536 B (2016) A/T/N: An unbiased descriptive classification
537 scheme for Alzheimer disease biomarkers. *Neurology* **87**,
538 539–547.
- [20] Balasa M, Gelpi E, Martín I, Antonell A, Rey M, Grau-
539 Rivera O, Molinuevo J, Sánchez-Valle R, Lladó A, Catalan
540 collaborative Study Group for FTD (2015) Diagnostic
541 accuracy of FTDC behavioral variant frontotemporal
542 dementia criteria in a clinicopathological cohort. *Neu-
543 ropathol Appl Neurobiol* **41**, 882–892.
- [21] Harris JM, Gall C, Thompson JC, Richardson AMT, Neary
544 D, du Plessis D, Pal P, Mann DMA, Snowden JS, Jones
545 M (2013) Sensitivity and specificity of FTDC criteria for
546 behavioral variant frontotemporal dementia. *Neurology* **80**,
547 1881–1887.
- [22] Dumurgier J, Gabelle A, Vercrusse O, Bombois S,
548 Laplanche J-L, Peoc'h K, Schraen S, Sablonnière B,
549 Pasquier F, Touchon J, Lehmann S, Hugon J, Paquet C
550 (2013) Exacerbated CSF abnormalities in younger patients
551 with Alzheimer's disease. *Neurobiol Dis* **54**, 486–491.
- [23] Cho H, Jeon S, Kang SJ, Lee J-M, Lee J-H, Kim GH, Shin
552 JS, Kim CH, Noh Y, Im K, Kim ST, Chin J, Seo SW, Na DL
553 (2013) Longitudinal changes of cortical thickness in early-
554 versus late-onset Alzheimer's disease. *Neurobiol Aging* **34**,
555 1921.e9-1921.e15.
- [24] Wallon D, Rousseau S, Rovelet-Lecrux A, Quillard-
556 Muraine M, Gyllen-Maréchal L, Martinaud O, Pariente J,
557 Puel M, Rollin-Sillaire A, Pasquier F, Le Ber I, Sarazin
558 M, Croisile B, Boutoleau-Bretonnière C, Thomas-Antérion
559 C, Paquet C, Moreaud O, Gabelle A, Sellal F, Sauvé

- 569 M, Laquerrière A, Duyckaerts C, Delisle M-B, Streichen-
570 berger N, Lannes B, Frebourg T, Hannequin D, Campion D,
571 collaborators of GMAJ project (2012) The French series
572 of autosomal dominant early onset Alzheimer's disease
573 cases: Mutation spectrum and cerebrospinal fluid biomark-
574 ers. *J Alzheimers Dis* **30**, 847–856.
- [25] Ishiki A, Kamada M, Kawamura Y, Terao C, Shimoda
575 F, Tomita N, Arai H, Furukawa K (2016) Glial fibrillar
576 acidic protein in the cerebrospinal fluid of Alzheimer's dis-
577 ease, dementia with Lewy bodies, and frontotemporal lobar
578 degeneration. *J Neurochem* **136**, 258–261.
- [26] Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E,
579 Bjerke M, Hölttä M, Rosén C, Olsson C, Strobel G, Wu E,
580 Dakin K, Petzold M, Blennow K, Zetterberg H (2016) CSF
581 and blood biomarkers for the diagnosis of Alzheimer's dis-
582 ease: A systematic review and meta-analysis. *Lancet Neurol*
583 **15**, 673–684.
- [27] Desgranges B, Kalpouzos G, Eustache F (2008) [Cerebral
584 imaging in healthy aging: Contrast with Alzheimer disease].
585 *Rev Neurol (Paris)* **164 Suppl 3**, S102-107.
- [28] Marelli C, Gutierrez L-A, Menjot de Champfleury N, Char-
586 roud C, De Verbizier D, Touchon J, Douillet P, Berr C,
587 Lehmann S, Gabelle A (2015) Late-onset behavioral variant
588 of frontotemporal lobar degeneration versus Alzheimer's
589 disease: Interest of cerebrospinal fluid biomarker ratios.
590 *Alzheimers Dement (Amst)* **1**, 371–379.
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