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CSF Biomarkers

# Late-onset behavioral variant of frontotemporal lobar degeneration versus Alzheimer's disease: Interest of cerebrospinal fluid biomarker ratios

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**Abstract**

**Introduction:** Cerebrospinal fluid (CSF) biomarker ratios were never evaluated in late-onset (>65 years) behavioral variant of frontotemporal lobar degeneration (bvFTLD) versus Alzheimer's disease (AD).

**Methods:** A retrospective monocentric study on 44 clinically suspected amnestic AD or bvFTLD patients with onset after 65 years and available CSF and clinical data.

**Results:** The final clinical diagnosis was AD (n = 28; 64%), late-onset bvFTLD (n = 14; 32%), and others (n = 2; 4%). Applying the CSF cutoff total-tau/$A\beta_{1-42}$ of 1.06, all the bvFTLD were in the FTLD range (<1.06, bvFTLD/FTLD), whereas the AD patients were either in the AD (>1.06, AD/AD) or in the FTLD range (<1.06, AD/FTLD); CSF biomarkers were significantly different in these three groups, but not neuroradiological features or presence of episodic memory deficit.

**Discussion:** Late-onset bvFTLD is underdiagnosed. The available CSF biomarker ratio cutoff need further improvement and overestimated late-onset bvFTLD but could potentially differentiate it from AD, notably in case of conflicting results.



*Keywords:* Alzheimer's disease; Frontotemporal lobar degeneration; Late-onset frontotemporal lobar degeneration; Cerebrospinal fluid; Biomarkers; Differential diagnosis

## 1. Introduction

The peculiar features of late-onset behavioral variant of frontotemporal lobar degeneration (bvFTLD), defined by a disease onset after 65 years, were recently described. Late-onset bvFTLD accounts for 3%–18% of all bvFTLD, and

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it is characterized by more frequent memory loss and hippocampal sclerosis and less cortical lobar atrophy than classical presenile-onset bvFTLD [1,2]. The latest bvFTLD International Consensus Diagnostic Criteria showed low sensibility for late-onset cases (73% for possible bvFTLD and 54% for probable bvFTLD), and Alzheimer's disease (AD) was the main misdiagnosis; the presence of "cerebrospinal fluid (CSF) biomarkers strongly indicative of Alzheimer's disease" is mentioned as exclusion criteria, without further details [3].

Comparative studies showed lower levels of CSF total-tau (T-tau) and phospho-tau-181 (P-tau) and higher level of $A\beta_{1-42}$ in frontotemporal lobar degeneration (FTLD) compared with AD [4–6]. The highest diagnostic accuracy in differentiating FTLD versus AD was obtained taking into account lower T-tau/$A\beta_{1-42}$ [6–8] and P-tau/$A\beta_{1-42}$ [8,9] ratios; some of these studies used autopsy-confirmed samples [6–8] and suggested cutoff values showed >80% sensitivity and specificity [6,9]. However, CSF biomarker analysis was never specifically applied to late-onset bvFTLD cases.

The aim of this study is to investigate whether CSF classical biomarkers and ratios could help in detecting late-onset bvFTLD and in differentiating it from AD.

## 2. Methods

### 2.1. Study sample

We performed a retrospective study (2007–2014) collecting patients with an initial clinical suspicion of amnestic AD or bvFTLD with onset after 65 years, from the CSF database of the Gui de Chauliac University Hospital (N = 518). All the patients signed a written informed consent approved by the local ethics committee (registered DC-2008-417). We considered only patients with available clinical and CSF data (n = 152). To limit possible confounding factors and alternative diagnosis, patients with psychiatric conditions able to explain the cognitive and behavioral alterations or with severe vascular burden (Fazekas score = 3) [10,11] were excluded, as well as patients with prominent aphasic or extrapyramidal presentations; 44 patients were finally retained.

CSF was collected in polypropylene tubes with standardized conditions [12]. CSF $A\beta_{1-42}$, T-tau, and P-tau were simultaneously measured in every sample using standardized commercially available Innotest sandwich ELISA according to manufacturer's procedures (Fujirebio Ghent Belgium).

### 2.2. Study design

The patients were initially classified as AD or late-onset bvFTLD on clinical basis only, according to the clinical core of the international criteria [3,13], and blind to CSF and imaging biomarkers; this classification was performed by a senior neurologist (CM).

We, then, integrated CSF and imaging results, according to the same international criteria [3,13]. Magnetic resonance imaging (MRI) were reviewed by a senior neuroradiologist (N.M.D.C.) for the presence of hippocampal atrophy (Scheltens score ≥2) [14], global or focal atrophy, parietal atrophy (Koedam score) [15], vascular white matter hyperintensities (Fazekas and Schmidt score) [10,11], and presence of cerebral microbleeds. Functional studies were performed with technetium-99m ($^{99m}$Tc) perfusion single-photon emission computed tomography (SPECT) and reviewed by a senior nuclear radiologist (D.D.V.).

Finally, a clinical follow-up (FU) was performed by a senior neurologist (C.M.), to establish a final clinical diagnosis of AD or late-onset bvFTLD.

At the end of this multistep diagnostic process, we applied the CSF T-tau/$A\beta_{1-42}$ >1.06 [6] and P-tau/$A\beta_{1-42}$ >0.2 [9] cutoff used for AD diagnosis and investigated whether these could contribute to the differential diagnosis. In case of discordance between the two ratios, the T-tau/$A\beta_{1-42}$ ratio was considered, due to higher specificity [6]. The interest of the Innotest Amyloid Tau Index (IATI) [16], a modified $A\beta_{1-42}$/T-tau ratio currently used in clinical practice, was also evaluated.

### 2.3. Statistical analysis

For samples description, quantitative variables were expressed as mean and standard deviation and qualitative variables as percentage. AD versus late-onset bvFTLD comparisons (Table 1) were performed with the Wilcoxon test for the quantitative, nonnormally distributed variables (age, FU duration, and cognitive scores); for qualitative variables, Fisher tests were used, after checking of the expected frequencies in each table cell (at least one was <5).

Samples comparison in the combined classification (Table 2) was performed with the nonparametric analysis of variance Kruskall-Wallis test and completed with the post hoc Nemenyi test to identify the significantly different group(s). The agreement between the four different diagnostic steps was estimated by the kappa coefficient [17]. A kappa value of <0.40 was considered a poor-to-fair agreement; 0.41–0.60, a moderate; 0.61–0.80, an acceptable; and 0.81–1.00, a perfect agreement. Statistical analysis was performed using SAS software, version 9.2 (SAS Institute).

## 3. Results

We selected 44 patients (F = 61%) with a mean age at onset of 70 ± 4 years; at the first examination (mean: 3 ± 2 years from disease onset), the mean score at the Mini-Mental State Examination (MMSE) was 20 ± 6/30, and mean score at the Mattis Dementia Rating Scale (Mattis DRS) was 114 ± 18/144.

Cerebral MRI or computed tomography (CT) studies were available for 36/44 patients (82%): MRI was performed in 29/44 patients and CT in 7/44. A $^{99m}$Tc SPECT study was available for 32/44 patients (73%).