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/Aβ1–42 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
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” was 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 Aβ1–42 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/Aβ1–42 [6–8] and P-tau/Aβ1–42 [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 Aβ1–42, 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 (99mTc) 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/Aβ1–42 >1.06 [6] and P-tau/Aβ1–42 >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/ Aβ1–42 ratio was considered, due to higher specificity [6]. The interest of the Innotest Amyloid Tau Index (IATI) [16], a modified Aβ1–42/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 99mTc SPECT study was available for 32/44 patients (73%).
3.1. Classification according to the international clinical core criteria

According to the international clinical core criteria (blind to radiological and CSF biomarkers), 26/44 (59%) patients were classified as AD, 14/44 (32%) as possible late-onset bvFTLD, 4/44 (9%) as both AD and late-onset bvFTLD, and 3/44 (7%) as neither AD nor late-onset bvFTLD (Fig. 1, diagnostic step 1). This classification showed a moderate agreement (k = 0.59 [0.29–0.88]) with the final after FU diagnosis.

3.2. Classification according to core clinical criteria and to radiological and CSF biomarkers

According to core clinical criteria and to structural (hippocampal or focal atrophy), metabolic (99mTc SPECT perfusion pattern), and CSF biomarkers (Fig. 1, diagnostic step 2), 26/44 (59%) patients were classified as possible or probable AD with high, intermediate, or uninformative biomarkers; 4/44 (7%) patients were classified as AD with frontal presentation; 11/44 (25%) patients were classified as possible or probable late-onset bvFTLD; and 3/44 (7%) patients remained “neither AD nor late-onset bvFTLD” (eTable 1). This classification showed a perfect agreement (k = 0.88 [0.72–1.00]) with the final after FU diagnosis. Classical CSF biomarkers Aβ1–42, T-tau, and P-tau allowed to better classify 8/44 patients (18%); four patients with a clinical diagnosis of late-onset bvFTLD were diagnosed as AD with frontal presentation (high CSF biomarkers probability for AD); four doubtful patients satisfying both AD and bvFTLD clinical criteria were diagnosed as bvFTLD (CSF biomarkers excluding an AD biological processes; Fig. 1, diagnostic step 2).

3.3. Final classification according to international criteria and after a clinical FU

After the FU (mean: 5 ± 3 years from disease onset; Fig. 1, diagnostic step 3), AD was diagnosed in 28/44 patients (64%), late-onset bvFTLD in 14/44 (32%), and corticobasal syndrome (CBS) in 1/44 (2%); in one patient, the diagnosis still remained undetermined (2%). In details, the diagnosis of AD was confirmed in 23/26 initial (diagnostic step 2) AD patients, although in three some atypical features were retained such as psychiatric problems (2/3), disinhibition (1/3), epilepsy (1/3), severe executive problems with perseverations (1/3), hallucinations (1/3), and hyperphagia (1/3); 2/26 AD were finally diagnosed as bvFTLD and in 1/26 AD patients, the final diagnosis remained undetermined; the four AD patients with frontal presentation were confirmed as well as the 11 initial (diagnostic step 2) late-onset bvFTLD patients. Of the three patients “neither AD nor late-onset bvFTLD,” one was finally diagnosed as AD, one as CBS, and one as late-onset bvFTLD. The comparison of clinical, radiological, and CSF biomarkers features between AD (n = 28) and late-onset bvFTLD (N = 14) according to the final after FU diagnosis (Table 1) showed no significant differences in age at onset, age at initial examination, mean FU duration, and presence of hippocampal memory deficit. The mean MMSE, but not the Mattis DRS score, was significantly lower in AD patients. Considering radiological data, no difference was found between the two groups about hippocampal or parietal atrophy; frontotemporal atrophy was nonsignificantly more frequent in the bvFTLD group (P = .07). As expected, the percentage of patients with altered CSF biomarkers was significantly different in the two groups (Table 1), as well as the mean CSF biomarker values (data not shown).

Table 1
Clinical, neuroradiological, and biological features of AD and late-onset bvFTLD patients (after the FU diagnosis according to the international criteria)

| Clinical, radiological, and biological features | Late-onset bvFTLD, n = 14/44 | AD, n = 28/44 | P value |
|-----------------------------------------------|-----------------------------|--------------|---------|
| Sex, F                                        | 6 (43%)                     | 20 (71%)     | .07     |
| Age at onset, y                               | 69 ± 3                      | 71 ± 5       | .23     |
| Age at initial examination, y                 | 72 ± 3                      | 74 ± 5       | .24     |
| Final FU duration, y                         | 5 ± 3                       | 4 ± 2        | .24     |
| MMSE                                         | 22 ± 5                      | 18 ± 5       | .02     |
| DRS Mattis                                   | 118 ± 20                    | 115 ± 14     | .29     |
| Hippocampal memory deficit                   | 10/14 (71%)                 | 26/28 (93%)  | .16     |
| Frontotemporal lobar atrophy, MRI            | 3/10 (30%)                  | 0/13 (0%)    | .07     |
| Parietal atrophy, MRI                        | 4/8 (50%)                   | 5/13 (38%)   | .67     |
| Hippocampal atrophy, MRI                     | 6/9 (67%)                   | 11/14 (79%)  | .64     |
| Positive 99mTc SPECT (according to diagnosis) | 10/14 (71%)                 | 12/19 (63%)  | NA      |
| Biological variables                         |                             |              |         |
| Aβ1–42 ≤700 pg/mL                            | 1/14 (7%)                   | 21/28 (75%)  | <.0001  |
| T-tau ≥400 pg/mL                             | 3/14 (21%)                  | 25/28 (89%)  | <.0001* |
| P-tau/Aβ1–42 ≤700 pg/mL and T-tau ≥400 pg/mL | 0                           | 19/28 (68%)  | <.0001  |

Abbreviations: AD, Alzheimer’s disease; bvFTLD, behavioral variant of frontotemporal lobar degeneration; FU, follow-up; MMSE, Mini-Mental State Examination; DRS, Dementia Rating Scale; MRI, magnetic resonance imaging; NA, not available.

Significant P value are in bold.

*Fisher test.

3.4. Classification according to CSF T-tau to Aβ1–42 cutoff

Considering the CSF T-tau/Aβ1–42 (AD range: >1.06; FTLD range: <1.06) and P-tau/Aβ1–42 (AD range: >0.2; FTLD range: <0.2) ratios (Fig. 1, diagnostic step 4), 29/44 (66%) patients had the two values in the FTLD range and 15/44 (34%) in the AD range; in only 3/44 patients, the two ratios were discordant with the T-tau/Aβ1–42 in the AD range and the P-tau/Aβ1–42 in the FTLD range. This classification showed a only moderate agreement (k = 0.43 [0.22–0.65]) with the final after FU diagnosis with a probable overestimation of the number of late-onset bvFTLD patients. The 29/44 patients with the T-tau/Aβ1–42
value in the FTLD range included 14 late-onset bvFTLD, 1 CBS, 1 undetermined case, and 13 AD (after FU diagnosis); the 15/44 patients with T-tau/Aβ1–42 in the AD range included 15 AD (after FU diagnosis; Fig. 1, diagnostic step 3 and 4). Of note, two patients considered as AD and one considered as “neither AD nor late-onset bvFTLD” at the very initial clinical evaluation (diagnostic step 1) had CSF ratio in the FTLD range and were confirmed as late-onset bvFTLD with CSF ratio in the FTLD range (n = 15/14); the “clinical AD/FTLD range” group, indicating the clinically diagnosed AD with CSF ratio in the FTLD range (n = 13/28); and the “clinical AD/AD range” group, indicating the clinically diagnosed AD with CSF ratio in the AD range (n = 15/28). These three groups did not show clinical or radiological differences. However, the three groups had a different percentage of patients with altered CSF biomarkers and the intermediate “clinical AD/FTLD range” most often had equivocal CSF alteration, with only 38% of the patients showing alteration in both Aβ1–42 and T-tau (Table 2). The analysis of the IATI results (Table 2) showed that the currently used cutoff of 1 would not be able to correctly differentiate AD versus bvFTLD patients. A more strict IATI values <0.8 were strongly, but not invariably, in favor of an AD diagnosis, whereas in this context an IATI value >1.2 was in favor of bvFTLD diagnosis. We can, therefore, conclude that the intermediate

### 3.5. Combined classification according to the final after FU diagnosis and T-tau to Aβ1–42 cutoff

The classification of the 44 patients combining data from the final after FU diagnosis and the T-tau/Aβ1–42 ratio (AD range: >1.06, FTLD range: <1.06; Table 2) allowed to separate the patients in three groups: the “clinical late-onset bvFTLD/FTLD range” group, indicating the clinically diagnosed late-onset bvFTLD with CSF ratio in the FTLD range (n = 14/14); the “clinical AD/FTLD range” group, indicating the clinically diagnosed AD with CSF ratio in the FTLD range (n = 13/28); and the “clinical AD/AD range” group, indicating the clinically diagnosed AD with CSF ratio in the AD range (n = 15/28). The three groups had a different percentage of patients with altered CSF biomarkers and the intermediate “clinical AD/FTLD range” most often had equivocal CSF alteration, with only 38% of the patients showing alteration in both Aβ1–42 and T-tau (Table 2). The analysis of the IATI results (Table 2) showed that the currently used cutoff of 1 would not be able to correctly differentiate AD versus bvFTLD patients. A more strict IATI values <0.8 were strongly, but not invariably, in favor of an AD diagnosis, whereas in this context an IATI value >1.2 was in favor of bvFTLD diagnosis. We can, therefore, conclude that the intermediate
IATI values between 0.8 and 1.2 were not very discriminant. Importantly, mean CSF biomarkers and ratios values were very significantly different in the three groups “clinical late-onset bvFTLD/FTLD range,” “clinical AD/FTLD range,” and “clinical AD/AD range” (Fig. 2), suggesting the possibility of further adjusting the cutoff to better separate and diagnose patients in the intermediate “clinical AD/FTLD range” group.

Of note, this three-group classification had also an important clinical correspondence as the patients in the intermediate “clinical AD/FTLD range” group had considerably more behavioral/cognitive clinical features of bvFTLD, defined according to the international criteria [3], than the group “clinical AD/AD range”, with the exception of the four AD patients with frontal presentation (Table 3).

None of the “clinical late-onset bvFTLD/FTLD range” patients had an alteration of the three biomarkers Aβ_{1-42}, T-tau, and P-tau at the same time, and 10/14 (71%) had the three biomarkers within normal limit, suggesting minor copathology in this group; 13/15 (87%) patients of the “clinical AD/AD range” group had an alteration of the three biomarkers at the same time; the intermediate “clinical AD/FTLD range” group had more variable results with 5/13 (38%) patients having the three CSF biomarkers altered at the same time (Table 2).

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Fig. 1. Multistep diagnostic process for each subject. Multistep diagnostic process, according to the different clinical, radiological, and biological parameters: each subject is represented as a part of the pie chart. The details of numbers of subjects and percentages for each diagnostic step are presented in the text. Abbreviations: AD, Alzheimer’s disease; bvFTLD, behavioral variant of frontotemporal lobar degeneration; CBS, corticobasal syndrome.

Fig. 2. Mean biomarkers values in the three groups of patients obtained on the basis of T-tau/Aβ_{1-42} ratio and final after FU diagnosis. Data expressed as mean ± SD. All the two-by-two comparisons are significant. Abbreviations: T-tau, total-tau; FU, follow-up; SD, standard deviation; bvFTLD, behavioral variant of frontotemporal lobar degeneration; FTLD, frontotemporal lobar degeneration; AD, Alzheimer’s disease; P-tau, phospho-tau-181; IATI, Innotest Amyloid Tau Index.

*Ratios (reference value = vertical axis on the right).
Table 3  
Behavioral and cognitive symptoms of bvFTLD in the 44 patients, according to the clinical after FU diagnosis and to the T-tau/Ab\textsubscript{1–42} CSF ratio

| Sex/AAO, y | FU at first evaluation, y | FU at final evaluation, y | Hippocampal memory loss | Perseverative, stereotyped, or compulsive ritualistic behavior | Apathy or inertia | Hyperorality and dietary changes | Neuropsychological dysexecutive profile | Loss of sympathy or empathy | Behavioral disinhibition | bvFTLD clinical features N/6 (initial FU) | bvFTLD clinical features N/6 (final FU) |
|------------|--------------------------|--------------------------|-------------------------|---------------------------------------------------------------|-----------------|-------------------------------|--------------------------------|----------------------------|---------------------------|--------------------------------|--------------------------------|
| F/72       | 1                        | 5                        | No                      | Yes                                                            | Yes             | Yes                           | Yes                          | Yes                        | Yes                       | 4                             | 4                             |
| M/68       | 2                        | 6                        | Yes                      | Yes                                                            | Yes             | Yes                           | Yes                          | Yes                        | Yes                       | 4                             | 4                             |
| F/67       | 10                       | 10                       | Yes                      | Yes                                                            | Yes             | Yes                           | Yes                          | Yes*                       | Yes*                      | 3                             | 4                             |
| M/69       | 2                        | 4                        | Yes                      | Yes                                                            | Yes             | Yes                           | Yes                          | Yes*                       | Yes*                      | 3                             | 4                             |
| F/75       | 0                        | 0                        | Yes                      | Yes                                                            | Yes             | Yes                           | Yes                          | Yes                        | Yes*                      | 3                             | 3                             |
| F/70       | 6                        | 7                        | Yes                      | Yes                                                            | Yes             | Yes                           | Yes*                         | Yes*                       | Yes*                      | 0                             | 3                             |
| F/69       | 1                        | 3                        | No                       | Yes                                                            | Yes             | Yes                           | Yes*                         | Yes*                       | Yes*                      | 4                             | 4                             |
| M/66       | 4                        | 9                        | Yes                      | Yes                                                            | Yes             | No                            | Yes                          | Yes*                       | Yes*                      | 2                             | 3                             |
| M/67       | 2                        | 2                        | Yes                      | Yes                                                            | Yes             | Yes                           | No                           | No*                       | Yes*                      | 3                             | 3                             |
| M/69       | 5                        | 7                        | Yes                      | Yes                                                            | Yes             | Yes                           | Yes                          | Yes*                       | Yes*                      | 3                             | 3                             |
| M/68       | 3                        | 4                        | Yes                      | Yes                                                            | Yes             | Yes                           | Yes*                         | Yes*                       | Yes*                      | 3                             | 3                             |

Continued
4. Discussion

Accurate antemortem FTLD diagnosis is crucial to the development and implementation of etiology-based therapies. In this article, we addressed the challenging problem of antemortem identification of late-onset bvFTLD patients and of the differential diagnosis from AD. As CSF biomarkers could give some insights about the underlying disease-causing neuropathologic process, we analyzed the interest of this analysis directly applied to this specific diagnostic problem.

On the basis of clinical, neuroimaging, and CSF biomarkers data at the initial evaluation and after a mean FU of 5 ± 3 years, we established a final diagnosis of late-onset bvFTLD in 14/44 patients (32%). Clinical and neuroimaging data confirmed that late-onset bvFTLD patients present many overlapping features with AD [1,2]. Indeed, the bvFTLD international criteria are known to be less sensitive for late-onset cases, which could therefore remain underdiagnosed.

As expected, CSF biomarkers were significantly different within the two groups. Of note, CSF classical biomarkers (Aβ1–42, T-tau, and P-tau) allowed to identify AD with frontal presentation and to exclude AD in some late-onset bvFTLD satisfying both AD and bvFTLD clinical criteria, improving final diagnosis in 8/44 patients (18%).

Different CSF biomarkers and cutoff for the FTLD versus AD diagnosis are available in the literature [5–7,9], and the T-tau/Aβ1–42 ratio is the most used. The T-tau/Aβ1–42 cutoff of 1.06 used in our study, obtained through an ELISA assay and pathologically or genetically validated, showed a sensitivity of 78.9% and a specificity of 96.6% in discriminating FTLD versus AD [6]. We also considered the P-tau/Aβ1–42 ratio of 0.2, showing a sensitivity of 91.7% and specificity of 92.6%, although not pathologically validated [9].

The application of the T-tau/Aβ1–42 CSF cutoff to our population resulted in 29/44 (66%) patients classified in the FTLD range and 15/44 (34%) in the AD range, showing a only moderate (κ = 0.43 [0.22–0.65]) correlation with the final after FU diagnosis: All the clinically diagnosed late-onset bvFTLD patients were in the FTLD range, whereas the clinically diagnosed AD patients were either in the AD (n = 12) or in the FTLD (n = 13) range. This suggested a probable overestimation of the number of late-onset bvFTLD in the group of clinically diagnosed AD. However, in three patients initially classified as AD (n = 2) or lacking definite diagnosis (n = 1), initial CSF ratios already supported the final after FU diagnosis of late-onset bvFTLD, further increasing the proportion of patients correctly classified on the basis of CSF results to 11/44 (25%). The CSF analysis could therefore still be considered very useful in differentiating late-onset bvFTLD from AD.

A closer analysis of CSF data clearly showed different average values of the CSF biomarkers in the three groups corresponding to the combined classification of the patients.

| Table 3: Behavioral and cognitive symptoms of bvFTLD in the 44 patients, according to the clinical after FU diagnosis and to the T-tau/Aβ1–42 CSF ratio (Continued) |
|---|
| Sex/AAO, y | FU at first evaluation, y | FU at final evaluation, y | Clinical fAD/AD T-tau to Aβ1–42 range | Clinical others/FTLD T-tau to Aβ1–42 range |
|---|---|---|---|---|
| F/68 | 1 | 2 | Yes | Yes |
| F/69 | 4 | 5 | No | Yes |
| M/70 | 0 | 3 | No | Yes |
| F/66 | 6 | 9 | Yes |
| M/70 | 0 | 3 | 3 | 3 |
| M/70 | 0 | 3 | 3 | 3 |
| M/70 | 0 | 3 | 3 | 3 |
| M/70 | 0 | 3 | 3 | 3 |
| M/70 | 0 | 3 | 3 | 3 |
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| M/70 | 0 | 3 | 3 | 3 |
according to the final after FU diagnosis and the T-tau/\(A\beta_{1-42}\) cutoff. These average values differences were confirmed for all the biomarkers and ratios tested and for the IATI index, currently used in clinical practice. The intermediate group “clinical AD/FTLD range” more often had equivocal CSF alterations. Importantly, this CSF distribution had also a clinical correspondence, in relation to the number of behavioral/cognitive clinical features of bvFTLD [3]: the patients in the intermediate “clinical AD/FTLD range” group were diagnosed as AD but had considerably more bvFTLD features than the group “clinical AD/AD range”.

Different reasons could explain why the available cutoff were not able to clearly separate AD from late-onset bvFTLD in the intermediate clinical AD/FTLD range group. First, the T-tau/\(A\beta_{1-42}\) cutoff was validated in autopsy proven classical presenile bvFTLD cases but not in late-onset cases [6]; in addition, the P-tau/\(A\beta_{1-42}\) cutoff was proposed to discriminated between AD and all the heterogeneous clinical variant of FTLD (primary progressive aphasia, bvFTLD, FTLD with parkinsonism) and is not specific for bvFTLD [9]. Second, preanalytical and analytical variables can lead to considerable variation in CSF biomarkers values determining problems in directly applying fixed cutoff from one laboratory to another [12,18,19]. The use of a ratio could also be discussed because of the challenge of having similar values, and not only the cutoffs, for \(A\beta_{1-42}\), T-tau, and P-tau in the different laboratories [20]; however, in the context of the specific diagnostic problem of bvFTLD versus AD, in which biomarker values are expected to be reciprocally inverses (\(A\beta_{1-42}\) lower in AD than in FTLD; T-tau and P-tau greater in AD than in FTLD), the use of a ratio is justified, as it may on the contrary smooth the variability intrinsic to each measure. Finally, a probabilistic approach, using cutoff ranges, could better reflect the difficulties and uncertainties of the antemortem diagnostic process in neurodegenerative diseases [21,22].

Anyway, the strength of the statistical difference among CSF biomarkers values in the three groups suggested that the actually proposed cutoffs are valuable and useful and that they could possibly be further improved taking into account the previously discussed considerations.

Of interest, in the clinical late-onset bvFTLD/FTLD range group, only 39% of subjects presented at least one altered CSF biomarker, suggesting in our late-onset cases less mixed pathology than expected [8]; however, we cannot exclude mixed pathology in the clinical AD/FTLD range group.

The lack of neuropathologic confirmation is an important limitation of this work, as in a large autopsy-confirmed dementia cohort, the use of the clinical diagnosis rather than neuropathologic diagnosis as the gold standard for evaluation of biomarker performance resulted in a 10%–20% underestimation of CSF T-tau and \(A\beta_{1-42}\) biomarker accuracy [8]. Moreover, the actually available biomarkers are mainly used to confirm or exclude the diagnosis of AD, and we still lack biomarkers specific for FTLD.

Genetic analysis, notably the progranulin plasmatic dosage and the MAPT and C9ORF72 genes analysis, is a possible alternative to neuropathology to obtain a definite bvFTLD diagnosis [3]; however, in the context of our population of mainly sporadic and late-onset cases, the diagnostic yield of these analyses is expected to be quite low.

The strength of our work is the careful and accurate clinical, radiological, and CSF biomarkers evaluation, in line with the most recent research criteria, applied for the first time to the specific context of the differential diagnosis between AD and late-onset bvFTLD. This study also shows the complexity of the antemortem diagnostic process in neurodegenerative diseases, requiring a multistep integration of different clinical, radiological, and biological information.

5. Conclusion

Late-onset bvFTLD is possibly underdiagnosed. We confirmed that clinical criteria do not sufficiently discriminate between late bvFTLD and AD, notably at initial disease stages. Moreover, we showed that structural and metabolic imaging biomarkers might not be very useful to detect late-onset bvFTLD cases. We showed that CSF biomarkers and ratios could be valuable in suggesting this diagnosis and differentiating it from AD, improving the diagnosis in 25% of cases. They could be particularly useful in case of atypical clinical features and in case of conflicting or borderline biomarkers results, although caution should be taken in interpreting CSF ratios results independently of the clinical context and of the other available biomarkers.

However, the actually available cutoff probably overestimates late-onset bvFTLD in our cohort; their accuracy should be further improved in relation to the population on study (late-onset disease) and using autopsy-confirmed samples. Moreover, a progressive standardization of CSF assays could ideally permit to generalize the obtained results. The use of a probabilistic approach with ratio cutoff ranges could also be useful in clinical practice.

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2. Interpretation: We present a multistep diagnostic process progressively integrating clinical and biomarker data; final diagnosis is based on International Criteria (McKhann et al. [13]; Rascovsky et al. [3]) and follow-up (mean 5 ± 3 years). Our analysis comparing and combining clinical diagnosis and CSF biomarker ratios suggests that late-onset bvFTLD is underdiagnosed; CSF biomarkers improve diagnosis in 25% of cases; clinical criteria and neuroradiological biomarkers are not sufficiently discriminative; CSF ratios analysis identified an intermediate clinical AD/FTLD ratio range group requiring further exploration.

3. Future direction: The accuracy of CSF ratio cutoff should be improved in relation to late-onset patients and autopsy-confirmed samples; we discuss the need of CSF assays standardization and the usefulness of a probabilistic approach with ratio cutoff ranges.

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