Chapter 7

IMPACT OF IMAGING AND CSF BIOMARKERS ON BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA DIAGNOSIS WITHIN A LATE ONSET FRONTAL LOBE SYNDROME COHORT

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ABSTRACT

**Background/Aims:** The criteria for behavioral variant Frontotemporal dementia (bvFTD) incorporate MRI and [18F ]FDG-PET. CSF is merely advised for excluding Alzheimer's disease. We aimed to assess the impact of biomarkers on diagnostic certainty and contingent changes of bvFTD diagnosis, within the clinically relevant neuropsychiatric differential diagnosis of subjects with a late onset frontal lobe syndrome (LOF).

**Methods:** We included 137 patients with LOF, aged 45-75, 72% males. Biomarker disclosure was considered contributing after any substantial difference in diagnostic certainty or a diagnostic change. Percentages of contributing biomarkers were compared between three major diagnostic groups (bvFTD, psychiatry, other neurologic disorder). Certainty levels in stable diagnostic groups were compared to those with a diagnostic change.

**Results:** Biomarker contributed in 53%, 60% and 41% of the LOF patients, for MRI, [18F ]FDG-PET and CSF respectively. Biomarkers changed the diagnosis in 14% of cases towards bvFTD and in 13% from bvFTD into an alternative. Those that changed had a lower level of a priori diagnostic certainty compared to stable diagnoses.

**Conclusion:** Our study not only supports the widely accepted use of MRI and [18F ]FDG-PET in diagnosing or excluding bvFTD, but also shows that CSF biomarkers aid clinicians in the diagnostic process.
INTRODUCTION

The behavioral variant of frontotemporal dementia (bvFTD) is a clinical syndrome consisting of progressive personality changes, behavioral disorders and deterioration of social cognition, executive functions, associated with specific frontal and/or temporal atrophy [1,2]. Revised Frontotemporal dementia consensus (FTDC) criteria incorporate a level of diagnostic confidence [3]. When the patient meets three out of six clinical core features a possible bvFTD diagnosis can be made. To fulfill probable bvFTD, apart from meeting possible bvFTD and signs of functional decline, prototypical structural or functional imaging abnormalities must be apparent [3]. A definite bvFTD diagnosis can only be made in the presence of a proven pathogenic mutation or after pathological confirmation [3]. Among the FTDC exclusion criteria for bvFTD are the presence of a psychiatric disorder and biomarkers strongly suggestive of underlying Alzheimer’s disease (AD).

BvFTD has a broad differential diagnosis of both neurodegenerative and psychiatric disorders, resulting in a similar late onset behavioral syndrome [4-13]. Although biomarkers take a prominent position in the present FTDC criteria, it is still unclear how they can distinguish between bvFTD and a representative control group [3]. Since most research focuses on differentiating bvFTD from either healthy controls or AD patients, it remains uncertain what role biomarkers might play in a clinically more relevant differential diagnostic group that includes psychiatric diagnoses as well as other neurological disorders. Imaging and CSF biomarkers separately are insensitive to a substantial part of the bvFTD patients and show overlap with imaging abnormalities in psychiatric disorders [14-22]. Therefore, we aimed to investigate the impact of the clinical package of ancillary investigation (MRI, [18F] FDG-PET and CSF biomarkers) on the differential diagnostic process of bvFTD and the effect these markers have on diagnostic certainty.

METHODS

Participants
Subjects were participants of the LOF-study (Late Onset Frontal lobe syndrome study), a multi-center observational cross-sectional and prospective follow-up study [23]. Inclusion in the cohort is symptom-based, where late onset frontal lobe syndrome (LOF) is defined as behavioral changes consisting of apathy, disinhibition, and/or compulsive/stereotyped behavior arising in middle or late adulthood observed by a clinician or reliable informant (defined by a Frontal Behavioral Inventory (FBI)-score of 11 or higher and / or a SRI Stereotypy Rating Inventory (SRI)-score of 10 or higher). 137 patients with a LOF, aged 45-75 years, were included through the memory clinic of the Alzheimer center (VU University Medical Center) and the Department of Old Age Psychiatry (GGZ InGeest Amsterdam).
between April 2011 and June 2013. Exclusion criteria were determined to establish a clinically relevant cohort of subject with recently developed late onset behavioral disturbances in which the behavioral complaints dominated the presentation. Exclusion criteria were an already established diagnosis of dementia or a psychiatric disorder that could explain behavior problems, a Mini Mental State Examination of <18, a medical history including traumatic brain injury, mental retardation, drugs and/or alcohol abuse, the absence of a reliable informant, insufficient communication skills, acute onset of behavioral problems, clinical apparent aphasia or semantic dementia, or MRI contraindications [23]. All patients underwent a standardized clinical assessment, consisting of behavioral and cognitive medical history, neurological and psychiatric exam, MMSE, frontal assessment battery (FAB), Montgomery-Asberg Depression Rating Scale (MADRS), Positive and negative symptom scale (PANSS), and a neuropsychological test battery [23]. Diagnosis was based upon the NIA-AA guidelines for Alzheimer’s disease, the NINDS-AIREN-criteria for vascular dementia, the international consensus diagnostic criteria for dementia with Lewy Bodies (DLB), the DSM-IV for psychiatric disorders and FTDC criteria for bvFTD [3;24-26].

Genetics
All patients with a positive family history for early-onset dementia were referred for clinical genetic counseling. Genetic screening included the MAPT, GRN, C9orf, PSEN1 and APP genes.

Neuro-imaging
All patients underwent a MRI-scan of the brain, acquired on a 3T Signa HDxt scanner (GE Medical Systems Milwaukee, WI) following a standard MRI protocol for dementia. An experienced neuroradiologist (F.B.) blinded to the patients' complaints and medical history visually assessed the MRI scans. He rated cortical atrophy, medial temporal lobe atrophy, and white matter hyperintensities systematically using appropriate scales [27-29]. The neuroradiologist also added a scan interpretation when appropriate (e.g. ‘normal aging’, ‘fitting a FTD diagnosis’ or ‘signs of neurodegeneration without a specific pattern’). In case of normal MRI findings or doubt on the interpretation of the abnormalities being explanatory for the behavioral changes an [18F]FDG-PET-scan was made. [18F]FDG-PET-scans were made on an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, USA). 185 MBq [18F] FDG was injected after subjects rested for 10 minutes with minimal noise and eyes closed in a dimly lit room. PET scans were acquired 45 minutes after injection during 15 minutes (3 frames of 5 minutes). [18F]FDG-PET-scans were assessed visually and interpreted by an experienced nuclear medicine physician based on the summed images of all the frames, blinded to the patients’ symptoms, complaints and medical history (B.v.B.).
CSF biomarkers

CSF was obtained with a lumbar puncture, performed according to a standard medical procedure in the lateral position in the L3-L4, L4-L5 or L5-S1 intervertebral space by a 25-gauge needle and syringe. CSF was collected in polypropylene tubes and centrifuged within an hour. The supernatant was stored in 0.5 ml aliquots at -20°C. Laboratory analysis of levels of total-tau (t-tau), phosphorylated-tau (p-tau) and amyloid-β 1-42 peptide concentrations took place using sandwich ELISA’s (Fujirebio/Innogenetics, Belgium) on a routine basis. Reasons for not obtaining CSF included technical difficulties, use of oral anticoagulants and patient refusal.

Level of diagnostic certainty and contribution of biomarkers

After the standardized clinical assessment a specialized neurologist (Y.P., N.P., P.S.) determined the most likely diagnosis and the level of diagnostic certainty (‘a priori’) using a diagnostic certainty scale, a visual analogue scale from 0-100 (quantitative variable). The neurologist was blinded to the results of the additional investigations (MRI, [18F]FDG-PET and CSF). In the same session, the clinical diagnosis was reconsidered taking the additional neuroimaging and CSF results into account, again scoring the level of certainty (‘a posteriori’, quantitative variable). For analysis the patients were grouped into the three major diagnostic outcome groups: possible, probable and definite ‘bvFTD’, ‘psychiatry’ and ‘other neurological disorders’ (OND). Each of the additional examinations (MRI, PET, CSF) was rated as ‘contributing’ versus ‘not- contributing’ to the eventual clinical diagnosis by the neurologist. Biomarkers were considered contributing (qualitative variable) by the neurologist when the certainty substantially changed (higher or lower) or the diagnosis itself changed due to the biomarker result. The patients with a change of diagnosis between bvFTD versus non-bvFTD (in both directions) were examined in more detail using logistic regression analyses.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows, version 20. Distribution of continuous variables was tested for normality and log-transformed when appropriate. Demographic baseline characteristics (age at presentation, disease duration, sex, education) were compared between the major diagnostic groups (bvFTD, psychiatry and all OND) using one way ANOVA tests. Percentages of contribution for MRI, [18F]FDG-PET and CSF were compared using Pearson’s χ2 test. Associations between the level of certainty and whether a change in diagnosis occurred were analyzed using logistic regression analyses. These associations were presented as odds ratio with 95% confidence interval (CI). Statistical significance was set at p < 0.05.
Medical ethical / informed consent
This study followed the Declaration of Helsinki on medical protocol and ethics and has been approved by the Medical Ethical Committee of the VU medical center Amsterdam, the Netherlands. All subjects gave written informed consent for the use of their data for research purposes.

RESULTS

Diagnostic groups a priori and a posteriori
In the 137 patients the a priori (before ancillary investigations) diagnoses were: 41.5% (n=57) bvFTD, 33% (n=45) psychiatry and 25.5% (n=35) OND. The majority of the psychiatric diagnoses were mood disorders (n=31). The most common OND were other dementia subtypes (n=23), like AD (n=7), vascular cognitive impairments (n=6) or DLB (n=3) (details on subdiagnoses have been published elsewhere [30].

In 27 patients the diagnosis changed after biomarker disclosure. This resulted in 43% (n=59) bvFTD (10 possible bvFTD, 47 probable bvFTD and 2 definite bvFTD diagnoses: one GRN mutation and one C9orf repeat expansion), 31% (n=43) with a psychiatric disorder and 26% (n=35) with OND (‘a posteriori’ diagnoses) (Table 1).

<table>
<thead>
<tr>
<th>a priori diagnosis</th>
<th>a posteriori diagnosis</th>
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<tbody>
<tr>
<td>bvFTD (n=57)</td>
<td>bvFTD (n=49)</td>
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<tr>
<td></td>
<td>psychiatry (n=1)</td>
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<td></td>
<td>psychiatry (n=5)</td>
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<tr>
<td></td>
<td>OND (n=24)</td>
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Table 1: Diagnosis before and after disclosure of imaging and CSF results
A posteriori diagnosis groups totals: bvFTD 59 (49+4+6), psychiatry 42 (1+37+5), OND 35 (7+4+24)

Demographics for the three major diagnostic groups (bvFTD, psychiatry and OND) are shown in Table 2. No significant group differences were found for age of onset, disease duration and years of education. The group of psychiatric patients contained significantly more males compared to the bvFTD group ($\chi^2 (1, N=102) = 6.18, p=.016$).
Impact of imaging and CSF biomarkers on behavioral variant frontotemporal dementia diagnosis

<table>
<thead>
<tr>
<th></th>
<th>bvFTD (n=59)</th>
<th>Psychiatry (n=43)</th>
<th>OND (n=34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong> (years) median (IQR)</td>
<td>58 (53-63)</td>
<td>58 (52-62)</td>
<td>61 (55-66)</td>
<td>p=.328</td>
</tr>
<tr>
<td><strong>Disease duration</strong> (years) Median (IQR)</td>
<td>3 (2-6)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td>p=.205</td>
</tr>
<tr>
<td><strong>Education</strong> (years) Median (IQR)</td>
<td>10 (9-14)</td>
<td>10 (10-14)</td>
<td>12 (9-15)</td>
<td>p=.065</td>
</tr>
<tr>
<td><strong>Sex</strong> (males (%))</td>
<td>36 (61)%*</td>
<td>36 (84)%*</td>
<td>26 (74)%</td>
<td>p=.043</td>
</tr>
</tbody>
</table>

Table 2: Demographics for diagnostic groups (‘a posteriori diagnosis’)

bvFTD: behavioral variant frontotemporal dementia, OND: other neurologic disease. IQR: interquartile range, 25th – 75th percentile. Age of onset: (F(2,133) = 1.123, p=0.328). Disease duration: (F(2,134) = 1.604, p=0.205). Education in years: (F(2,132) = 2.786, p=0.065). Sex: χ2 (2, N=137) = 6.47, p=.043). Results with * differ significantly.

Imaging and CSF biomarker collection and contribution

All 137 LOF subjects (100%) underwent MRI scanning. An [18F]FDG-PET-scan was made in 96 of the 137 patients (70%). In 107 of the 137 patients (78%) CSF had been obtained. The neurologists rated MRI as contributing in 72 (53% of 137) patients, [18F]FDG-PET as contributing in 58 (60% of the 96) patients and CSF as contributing in 44 (41% of the 107) patients. The neurologist explicated that the MRI results increased diagnostic certainty in 49 cases, decreased certainty in 12 cases and changed the diagnosis in 11 cases. The neurologist explicated that the [18F]FDG-PET results increased diagnostic certainty in 32 cases, decreased certainty in 17 cases and changed the diagnosis in 9 cases. The neurologist explicated that the CSF results increased diagnostic certainty in 29 cases, decreased certainty in 13 cases and changed the diagnosis in 2 cases.

Contribution of biomarkers diagnostic subgroups

Contribution of biomarkers was separately investigated for the three major diagnostic groups: bvFTD patients, psychiatric patients and patients with OND. Group differences in numbers of MRI, [18F]FDG-PET and CSF examinations that were rated as contributing were compared and are shown in Table 3. There were no significant differences between the diagnostic groups concerning the frequency in which the MRI and the [18F]FDG-PET were rated as contributing (Pearson χ2 (2, N=137) = .830, p=.760 and Pearson χ2 (2, N=96) =1.803, p=.417, respectively). The absence or presence of abnormal CSF biomarkers, however, was considered contributing more often in subjects with a psychiatric diagnosis compared to the OND group (χ2 (1, N=60)= 6.058, p = 0.019) (overall test, df 2, Table 3).
Table 3: Group differences in number of MRI, FDG-PET and CSF examinations that contributed to the diagnosis

<table>
<thead>
<tr>
<th></th>
<th>bvFTD (n=59)</th>
<th>psychiatry (n=43)</th>
<th>OND (n=34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI contributing</td>
<td>29 (49%)</td>
<td>25 (58%)</td>
<td>18 (51%)</td>
<td>p=.760</td>
</tr>
<tr>
<td>FDG-PET contributing</td>
<td>24 (60%)</td>
<td>17 (53%)</td>
<td>17 (71%)</td>
<td>p=.417</td>
</tr>
<tr>
<td>CSF contributing</td>
<td>17 (36%)</td>
<td>20 (59%)*</td>
<td>7 (27%)*</td>
<td>p=.028</td>
</tr>
</tbody>
</table>

bvFTD: behavioral variant frontotemporal dementia, OND: other neurologic disease. MRI contributing: $\chi^2 (2, N=137) = 0.830, p=0.760$. FDG-PET contributing: $\chi^2 (2, N=96) = 1.803, p = 0.417)$. CSF contributing: $\chi^2 (2, N=107)= 7.041, p = 0.028$. Results with * differ significantly.

Change of diagnosis after disclosure biomarker results

In a total number of 18 patients the diagnosis changed either towards bvFTD or from bvFTD to another diagnosis after disclosure of the additional test results (Table 1). After the biomarker results were disclosed, 8 of the 57 bvFTD diagnoses (14%) were changed to a non-bvFTD diagnosis (1 towards a psychiatric diagnosis and 7 to OND). On the other hand, in 10 out of 80 subjects of the non-bvFTD group (13%) diagnosis was changed to bvFTD (4 from a psychiatric diagnosis and 6 from OND) (Table 1).

Diagnostic change associated with low level of certainty

Median a priori level of diagnostic certainty in the total LOF cohort was 85 (IQR 73-91) and increased to a median of 92 (IQR 81-98) after disclosure of the neuroimaging and CSF results (rated on diagnostic certainty scale running from 0-100). In 98 cases (72%) the level of certainty increased, whereas in 28 (20%) cases the level of certainty decreased. In 11 cases (8%) the level of diagnostic certainty remained stable. Figure 1 shows the level of diagnostic certainty before and after biomarker disclosure for bvFTD and non-bvFTD patients. Patients in which the diagnosis was changed from bvFTD towards another diagnosis (n=8) had a significant lower a priori level of certainty compared to all other patients (OR 1.57 (95% CI 1.04 – 2.38). The chance of having a stable bvFTD diagnosis strongly increased per every 5-points increase of the a priori diagnostic certainty scale, expressed per every 5 points considering the small step scale (OR 9.54).

The group of patients in which the diagnosis was changed towards bvFTD (n=10) had a lower a priori level of certainty (median 82, IQR 63-91) compared to those with a bvFTD diagnosis all along (OR 1.08, 95% CI 1.01 – 1.16). This results in an OR of 1.47 of a stable non-bvFTD diagnosis per every 5 points increase in a priori diagnostic certainty. All odd ratios were adjusted for sex, disease duration, education and age of onset.
Influence of biomarkers in change of diagnosis

When we restricted the analysis to those patients in which a change of diagnosis was made (n=27) the percentages in which the MRI and CSF were considered useful were comparable to all other patients: 59% (n=16) of the MRIs and 36% (n=8) of the CSF biomarker results contributed to the diagnosis according to the neurologist (Table 1, Figure 1). Of these 8 patients 5 had normal CSF biomarker values (making neurodegeneration less probable or raising probability of a prior considered psychiatric diagnosis), 1 had an AD profile and 2 had isolated elevated t-tau levels, suggestive of neuronal loss. In the group with a diagnostic change the [18F]FDG-PET scan was considered contributing to the diagnosis more often (82%, n=18) compared to patients with stable diagnoses (Pearson χ2 (1, N=96)=5.47, p=.03).

Figure 1: Diagnostic certainty (range 50-100) before (dark grey) and after (light grey) additional investigations were known: groups are organised by whether diagnosis was stable or changed (bvFTD versus non-bvFTD)

bvFTD: behavioral variant frontotemporal dementia

DISCUSSION

This study shows that MRI, [18F]FDG-PET and CSF biomarkers each play a contributory role in the clinical differential diagnostic process of bvFTD, both by providing biomarker evidence for this diagnosis as well as by excluding the diagnosis. In our study, particularly in those patients in which there was a low level of certainty due to ambiguity about a differential diagnostic option, the imaging and CSF examinations had an added value
according to specialized neurologists (in 41-60% of examinations). The most striking increase in certainty was seen in the patients with an a priori bvFTD diagnosis with a low level of certainty in which the diagnosis was changed towards a non-bvFTD diagnosis, based on the biomarker results.

Our study not only supports the widely accepted use of MRI and \[^{18}F\]FDG-PET in diagnosing or excluding bvFTD, but also shows that CSF biomarkers add to this diagnostic process, even though these markers are not included in the consensus criteria in that matter. CSF results can either be useful for excluding (or confirming) an AD diagnosis, or can give rise to a suspected bvFTD or psychiatric diagnosis (usually in case of normal CSF biomarkers), depending on what the specific differential diagnosis is in each particular patients. In a minority of subjects CSF examinations contributed to a change of diagnosis.

It has been shown by others that neuroimaging findings may be inconclusive in bvFTD patients [19;31]. MRI scanning of the brain reveals disproportional atrophy in medial frontal, orbital-insular and anterior temporal regions in 50-70% of bvFTD patients [19]. In a neuropathologically confirmed cohort, only 50% of the FTLD subjects had MRI abnormalities consistent with an FTD diagnosis [18]. Accordingly with this limited sensitivity, in a proportion of our patients the imaging results were either inconclusive or matter of discussion. The use of MRI for bvFTD may also be limited because of abnormalities with regard to psychiatric disorders, occasionally displaying similar imaging abnormalities, reducing the specificity [20;21;32-34]. This must be taken into account when differentiating between bvFTD and psychiatric disorders. \[^{18}F\]FDG-PET with visual rating supposedly increases imaging sensitivity to 81% up till 90% [19]. But when the added value of \[^{18}F\]FDG-PET was examined in clinical bvFTD patients with a normal structural MRI, the sensitivity was only 47% (with a specificity of 92%) [35]. Our data do suggest an added value of \[^{18}F\]FDG-PET in this patient group, but the specificity might be lower than reported when including a psychiatric differential diagnosis. It must be noted that in our study patients with a clear atrophy pattern on MRI, fitting a bvFTD diagnosis, did not undergo an \[^{18}F\]FDG-PET-scan. This results in a selection bias and may underestimate the added value of \[^{18}F\]FDG-PET in our cohort. However, since the same selection takes place in clinical practice, we did follow the approach of the memory clinic routine.

Measuring CSF biomarkers (amyloid-beta, total-tau and phospho-tau (p-tau)) is mainly considered helpful to distinguish FTD from AD. No specific CSF biomarker pattern has been identified for FTD [14-17]. A higher total-tau level has been associated with a subgroup of FTD patients without pathogenic mutations with a relative fast rate of progression [36]. Also, recently, a decreased phospho-tau-181/total-tau ratio differentiated FTD with underlying TDP-43 pathology from FTD with underlying tau-pathology [37]. These findings need to be confirmed, but indicate an increasing potential use of CSF biomarkers in bvFTD diagnosis, for now in a research setting. In psychiatric disorders like depression and schizophrenia CSF total-tau and p-tau levels vary between normal to
slightly elevated compared to healthy controls, but are overall significantly lower than seen in AD [38-40]. Older schizophrenia subjects showed to have lowered amyloid-beta levels compared to healthy controls, but higher than seen in AD patients and in this particular study group tau-levels were normal [41].

Consequently, clinical practice still lacks a biomarker with perfect discriminating qualities when it comes to bvFTD and the heterogeneous disorders also resulting in a frontal lobe syndrome [3;42]. Therefore, biomarkers are still only an aid to be used in combination with clinical assessment. The field of neurodegenerative biomarkers is still emerging and the practical use is a topic of debate. Our study measures the impact of the total package of biomarkers in a clinical setting. Although the usage of a visual analogue scale is subjective, and as a consequence, no quantitative measures are available to estimate the influence of each separate biomarker on the diagnostic certainty. Nonetheless, this approach does results in ecologically valid data and gives rise to interesting starting points for future studies.

Interestingly, a change of diagnosis into bvFTD was as common as from bvFTD to an alternative diagnosis. This finding stresses that not only a psychiatric misdiagnosis (in case of bvFTD) is a pitfall to recognize, but also a bvFTD diagnosis in case of a psychiatric disorder could be an increasingly common scenario due to improved awareness of bvFTD [43].

Among the strengths of our study is the symptom based inclusion, since in clinical routine patients present with a symptom, not with a diagnosis. Furthermore, this way we were able to investigate the diagnostic process of bvFTD within its clinically highly relevant ‘frontal’ differential diagnoses, instead of merely comparing bvFTD to AD or healthy controls. The diagnostic process we followed, consisting of clinical judgment of the behavioral presentation followed by the interpretation of neuroimaging and CSF results, closely approaches clinical practice, although using CSF in bvFTD diagnosis is at present still reserved for research settings. Another strength is the recruitment of patients via the neurology based memory clinic as well as the psychiatric clinic in order to avert referral bias. It must be noted though, that our study was performed in a tertiary center. Therefore, the a priori certainty levels are expected to be relatively high, which is clearly illustrated by our results. This results in a relatively small difference between the a priori and a posteriori certainty and thereby in lower levels of contribution of imaging and CSF markers. A likely consequence is underestimation of the added values of these examinations. Furthermore, a limitation of the study is the absence of neuropathological confirmation. Therefore, clinical follow up of the cohort is needed to strengthen the used gold standard of clinical consensus diagnosis with ideally several years of follow-up or neuropathological confirmation. Unfortunately, in our study no data on interrater variability and interrater agreement were available, limiting the generalizability of the results.

Other limitations must be taken into account. Recent literature has shown that patients with the C9orf72 repeat expansion can present with prominent psychiatric symptoms,
minimal atrophy and show slow progression and can therefore easily be mistaken for a psychiatric disorder [44]. Systematic screening for C9orf72 in all patients would be interesting for future analyses of the cohort. Furthermore, the so called phenocopy syndrome, possibly without a neurodegenerative origin, can mimic real bvFTD [45-47].

The recently developed FTDC criteria are a great step forward, incorporating neuroimaging to determine the level of diagnostic certainty [3]. Nonetheless, our data suggest that more research is needed since future diagnostic guidelines might benefit from incorporating CSF results as well. Since bvFTD is progressive and will eventually lead to death whereas psychiatric disorders are treatable, every biomarker adding to the correct discrimination between the two would be essentially contributing [48].

To establish more clarity about the sensitivity and specificity of the established CSF biomarkers, prospective clinical research with CSF data of FTLD patients and the clinically relevant control groups, including psychiatric disorders, must be conducted.
REFERENCE LIST


