The frontal lobe syndrome

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Chapter 6

IDENTIFYING BVFTD WITHIN THE WIDE SPECTRUM OF THE LATE ONSET FRONTAL LOBE SYNDROME: A CLINICAL APPROACH

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ABSTRACT

Objectives: The behavioral variant of frontotemporal dementia (bvFTD) can be difficult to diagnose due to the extensive differential diagnosis, including many other diseases presenting with a frontal lobe syndrome. We aimed to identify the diagnostic spectrum causing a late onset frontal lobe syndrome (LOF) and examine the quality of commonly used instruments to distinguish between bvFTD and non-bvFTD patients, within this syndrome.

Methods: 137 patients fulfilling the criteria of LOF, aged 45-75 years, were included in a prospective observational study. Diagnoses were made after clinical and neuropsychological examination, and neuroimaging and cerebral spinal fluid results were taken into account. Baseline characteristics and the scores on the MMSE, frontal assessment battery (FAB), Frontal Behavioral Inventory (FBI) and Stereotypy Rating Inventory (SRI) were compared between the bvFTD and the non-bvFTD group.

Results: Fifty-five (40%) of the patients received a bvFTD diagnosis (33% probable and 7% possible bvFTD). Fifty-one patients (37%) had a psychiatric disorder, including 20 with major depressive disorder. Thirty-one patients received an alternative neurological, including neurodegenerative, diagnosis. MMSE and FAB scores were unspecific for a particular diagnosis. A score above 12 on the positive FBI subscale or a score above 5 on the SRI were indicative of a bvFTD diagnosis.

Conclusions: A broad spectrum of both neurological and psychiatric disorders underlies a late onset frontal lobe syndrome, of which bvFTD was the most prevalent diagnosis in our cohort. The commonly used MMSE and the FAB could not successfully distinguish between bvFTD and non-bvFTD, but this could be achieved with the more specific FBI and SRI.

INTRODUCTION

The behavioral variant of Frontotemporal dementia (bvFTD) is a neurodegenerative disorder that predominantly affects the frontal and temporal lobes of the brain. BvFTD usually presents between the fourth and sixth decade in life and is expressed by progressive personality and behavioral changes and deterioration of social cognition and executive functions [1-3]. The frontal behavioral changes are insidious at the early disease stages of bvFTD. According to the recently established international consensus criteria, 3 out of 6 core criteria are mandatory for a bvFTD diagnosis [4]. Five of these core criteria are behavioral. Previously, we have coined these frontal symptoms, arising above the age of 40, as 'late onset frontal lobe syndrome' (LOF) [5].

Apart from bvFTD, a variety of other clinical disorders may in their turn cause a similar LOF. Cerebral infarction, hemorrhage, intracerebral or intracranial extracerebral tumors and traumatic brain injuries may (acutely) damage the brain tissue causing a combination of frontal lobe syndrome features. These features can also arise in Alzheimer's disease (AD), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Parkinson's disease dementia, vascular dementia (VaD) and multiple sclerosis (MS) [6-15]. Moreover, LOF may occur in psychiatric disorders since dysfunction of prefrontal-subcortical circuits, may result in apathy and psychomotor retardation in depressive disorder, disinhibition in psychosis/schizophrenia or repetitive behavior in obsessive compulsive disorder (OCD) [16-19]. Identifying bvFTD and differentiating it from other LOF etiologies can be difficult in clinical practice due to the great overlap in clinical presentation between these disorders and the widespread age of onset. This is illustrated by the fact that a high proportion of bvFTD patients initially receives a psychiatric diagnosis [19;20]. But, if 'behavioral disturbance is better accounted for by a psychiatric diagnosis', a diagnosis of bvFTD has to be excluded according to the consensus criteria [4]. In clinical practice, this delays the process of correctly diagnosing the etiology of the behavioral symptoms [18]. BvFTD is neuropsychologically characterized by executive dysfunction with relative sparing of memory and visual spatial functioning, but a subset of bvFTD patients has prominent memory impairment or no specific dysexecutive profile compared to AD patients [3;4;21;22]. In fact, bvFTD patients can have impairment in nearly all cognitive domains as well as on a global cognitive screening scale [22;23]. However, at an early stage, bvFTD patients may show remarkably little abnormality on neuropsychological tests [24].

The Mini-Mental State Examination (MMSE) and the Frontal Assessment Battery (FAB) are among the most widely used short screening instruments. A FAB cut-off of 12 has shown a sensitivity of 77% and a specificity of 87% for bvFTD versus AD [25;26]. The Frontal Behavioral Inventory (FBI) and the Stereotypy Rating Inventory (SRI) show more promise in differentiating bvFTD from AD. The FBI can differentiate bvFTD patients from

AD and from a more heterogeneous differential diagnostic group [27;28]. The SRI scores differentiated bvFTD patients from healthy controls, AD and VaD patients [29]. However, it remains unclear if these four screening instruments are able to differentiate between bvFTD and the clinically more relevant psychiatric differential diagnosis.

Since neurodegenerative disorders are progressive and will eventually lead to death whereas most psychiatric disorders are treatable, prognosis and management differ greatly between bvFTD and the differential diagnosis. Therefore, developing instruments to discern the two is of great importance.

The late onset frontal lobe syndrome (LOF-)study is the first prospective observational study with a symptom-based inclusion [5]. This study is therefore suitable to approach clinical practice and investigate the clinical problem. The first goal is to explore the causes of LOF in a memory clinic and in a psychiatry based cohort. Secondly, we examined whether widely used frontal or cognitive screening instruments (MMSE, FAB and more specific behavioral inventories developed for bvFTD diagnosis: FBI, SRI) could differentiate between bvFTD and other causes of a LOF [25;29-31].

METHODS

Patients

The Late Onset Frontal lobe syndrome (LOF)-study is an observational prospective multi-centre cohort study designed to examine early discrimination of bvFTD from other neurological and psychiatric disorders in subjects with symptoms of late onset frontal lobe syndrome (apathy, disinhibition, compulsive behavior) [5]. LOF patients were recruited through the memory clinic of the Alzheimer center of the VU University Medical Center and the in- and out-patients department of Old Age psychiatry of GGZinGeest, Amsterdam, the Netherlands, between April 2011 and June 2013. Two year follow up assessments are still ongoing.

LOF was defined as behavioral change consisting of apathy, disinhibition and / or compulsive / stereotypical behavior arising in middle or late adulthood (45-75 years) as observed by the clinician or a reliable informant, with a total (negative and positive subscale added) FBI-score of 11 or higher and / or a-score of 10 or higher. Exclusion criteria were: (1) an already established dementia or psychiatric diagnosis which could explain the behavioral problems (2) MMSE-score ≤ 18 (3) medical history including traumatic brain injury, mental retardation, drugs abuse or alcohol abuse of more than 3 units a day (4) lack of reliable informant (5) insufficient communicative skills of either patient or the closest informant (language, serious hearing impairment or behavioral disturbances including threatening or physical aggression) (6) acute onset of behavioral problems (7) clinically apparent aphasia or semantic dementia (8) MRI contraindications.

A total of 234 patients with a LOF was screened for eligibility. Ninety-seven of these patients were excluded based on: alcohol or drug abuse (present or past) (n=41), a severe language problem (n=6), acute onset of complaints (n=6) or either refusal or incapability to complete baseline measurements (due to disease severity, aggression or logistics) (n=44). The remaining 137 patients were included in the LOF-study. Data on demographics was collected at inclusion: age, sex, disease duration up till presentation and the number of years of education. All subjects underwent a neuropsychological test battery and an MRI-scan. Diagnosis was based upon the NIA-AA guidelines for AD, the NINDS-AIREN-criteria for VaD, the International bvFTD Criteria Consortium (FTDC), the McKeith criteria for DLB and the NINDS-Society for Progressive Supranuclear Palsy criteria for PSP [32-37]. 'Possible bvFTD' was diagnosed in cases fulfilling clinical bvFTD criteria without support of neuroimaging findings and lacking an alternative (neurological or psychiatric) diagnosis. Psychiatric diagnosis was established by an experienced psychiatrist and based upon the DSM-IV for psychiatric disorders. Final consensus diagnosis was the result of combining these guidelines and criteria with the clinical examination of the neurologist, the clinical examination of the psychiatrist, the imaging and CSF results and a neuropsychiatric test battery in a multidisciplinary meeting.

A more detailed description of the diagnostic procedure has been published previously [5].

For the main analyses, diagnoses were clustered into two major groups: bvFTD and non-bvFTD.

Imaging and CSF biomarkers

MRI scanning was performed on a 3T Signa HDxt Scanner (GE Medical Systems Milwaukee, WI) following a standard MRI protocol for dementia. The MRI-scans were systematically rated by an experienced neuroradiologist blinded to the patients' complaints and medical history. Specific FTD features like mesio-frontal, orbito-frontal and temporal atrophy were rated. Other MRI parameters (global cortical atrophy, medial temporal lobe atrophy, posterior cortical atrophy and white matter hyperintensities) were scored using appropriate scales [38-40]. In case of normal MRI results or doubt on the interpretation of the abnormalities being explanatory for the behavioral changes an [^{18}F]FDG-PET-scan was made. This was the case in 96 patients. [^{18}F]FDG-PET-scans were made on a ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, USA). All PET-scans were rated and judged by a nuclear medicine physician blinded to the patients' complaints and medical history. The majority of patients (n=107) also underwent a lumbar puncture [5]. A tau/Ab42 ratio of > 0.52 was considered a cerebrospinal fluid profile suggestive of Alzheimer's disease pathology [41]. An isolated elevated total tau-level was considered indicative for neuronal loss.

Screening instruments

We studied the quality to differentiate between bvFTD and other neurological or psychiatric syndromes of 4 instruments: the MMSE, FAB, FBI and the SRI.

The MMSE was developed as a screening instrument, grading cognitive impairment and has been widely applied for differentiating dementia patients from controls (scores range from 0 to 30, with higher scores indicating better performance) [30]. Although affected by demographic factors, the MMSE has moderate to high reliability and validity [42]. Since the MMSE is insensitive for frontal-subcortical dysfunction, the FAB was specifically designed to detect these disturbances (scores range from 0 to 18, with higher scores indicating better performance). The FAB also has good reliability and validity [25;43].

The FBI and SRI are two informant-based behavioral questionnaires, developed to identify bvFTD. The FBI consist of a negative (e.g. apathy, indifference or loss of insight) and a positive symptom subscale (e.g. inappropriateness, aggression or hyperorality) and scores range from 0 to 72, with higher scores indicating severe behavioral disturbances (see: Appendix 1). FBI cut off values have been reported that vary from 15 up till 27, depending on which control group (usually AD) was used and whether the study maximized either sensitivity or specificity [27;28]. The FBI seems to measure frontal dysfunction and a low cut-off value was therefore used for inclusion in the LOF study; it has shown good discriminative properties, a high interrater reliability and high item consistency when tested in bvFTD versus AD and other dementias [27]. The FBI has not been examined in the psychiatric differential diagnosis of bvFTD yet.

The SRI assesses five distinct stereotypic behavioral disturbances often seen in patients with bvFTD: disturbances in eating and cooking behaviors, roaming, speaking, movements, and daily rhythm (see: Appendix 2). In scoring the SRI both the frequency and the severity of each behaviour are determined (with a maximum of 12 per item resulting in a maximum score of 60) and the scores of FTD patients showed promise in differentiating them from healthy controls, AD and VaD patients [29]. The SRI shows a high level of validity, internal consistency, inter-rater and test-retest reliability [29].

The screening instruments were not used in the diagnostic process in order to avoid circularity.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows, version 20. Demographic baseline characteristics were compared between bvFTD and non-bvFTD subjects. Distribution of continuous variables was checked for normality, log-transformed and tested non-parametrically when appropriate. Pearson Chi-square tests, Mann-Whitney U test or Two-sample t-tests were used as appropriate to compare groups. Logistic regression analyses were used to investigate the association between the MMSE, FAB, FBI and SRI (independent variables) and the diagnostic group (dichotomous dependent

variable: bvFTD versus non-bvFTD). The assumptions for logistic regression analyses were tested, and continuous variables were categorized into quartiles if they did not show a linear relationship with the dependent variable. Subsequently, we performed univariable and multivariable logistic regression analyses with age and sex as covariates. Associations were presented as odds ratios with 95% confidence intervals (CI). To investigate the quality of the screening instruments to differentiate between groups, additional to sociodemographics (age and sex), we composed receiver-operating characteristic (ROC) curves and calculated the area under the curves (AUC) with 95% CI for the multivariable logistic regression models of the different screening instruments. An AUC of 0.5 was considered to demonstrate no discriminatory quality and an AUC of 1.0 perfect discrimination [44]. An AUC between 0.5 and 1.0 was considered as follows: 0.5-0.6 *fail*, 0.6-0.7 *poor*, 0.7-0.8 *fair*, 0.8-0.9 *good* and 0.9-1.0 *excellent*. Exploratory analyses were performed to reveal possible masking of results due to the heterogeneity of the non-bvFTD group: all analyses were repeated with three major outcome groups (FTD, neurology or psychiatry) instead of two (bvFTD and non-bvFTD).

Results were considered to be statistically significant if $p < 0.05$.

Medical ethical / informed consent

This study followed the Declaration of Helsinki on medical protocol and ethics. The Medical Ethical Committee of the VU University Medical Center Amsterdam, the Netherlands, approves the study. All subjects gave written informed consent for the use of their clinical data for research purposes.

RESULTS

Diagnosis

BvFTD (possible or probable) was the most prevalent diagnosis (n=55, 40%). A non-bvFTD diagnosis was made in 82 patients (60%) (Table 1 and Figure 1). This non-bvFTD group could be subdivided into neurological and a psychiatric group. Examining the diagnoses in more detail showed that a heterogeneous spectrum of etiologies underlied LOF in our cohort: possible bvFTD was diagnosed in 10 (7%) and probable bvFTD was diagnosed in 45 (33%) patients (Figure 1). 21 of these 45 patients (15% of the total LOF cohort) showed frontal and/or temporal atrophy on the MRI and the remaining 24 patients (18%) showed frontal and/or temporal hypometabolism on the FDG-PET [4]. The second most prevalent diagnosis was a major depressive disorder (n=20, 15%), followed by possible bvFTD (n=10, 7%). Only 7 patients with a major depressive disorder had a psychiatric mood disorder at some time in their medical history (range 6-40 years ago). In the remaining 13 patients the current depressive episode is the first mood disorder.

Other neurodegenerative illnesses constitute an important part of the diagnoses (AD, DLB, VaD, (vascular) MCI). Apart from the depressive disorder, a broad spectrum of psychiatric diagnosis (schizophrenia, bipolar disorder, anxiety disorder) and a small minority of psychological conditions (marital problems) were found to be explanatory for LOF. In 3% no satisfactory explanation for the LOF was found (Table 1).

Diagnosis	n	percentage of total
bvFTD		
probable bvFTD	45	33%
possible bvFTD	10	7%
Neurology		
AD	7	5%
DLB	3	2%
vascular dementia	2	1.5%
vascular MCI	4	3%
other dementia	7	5%
other neurology	8	6%
Psychiatry		
major depression	20	15%
minor depression	5	4%
schizophrenia	2	1.5%
bipolar disorder	6	4%
anxiety disorder	1	1%
marital / relational	3	2%
OCD	2	1.5%
personality disorder	2	1.5%
autism spectrum disorder	3	2%
other psychiatry	3	2%
no explanation	4	3%

Table 1: Count diagnostic groups (n=137)
bvFTD: behavioral variant frontotemporal dementia, AD: Alzheimer's disease, DLB: dementia with Lewy bodies, MCI: mild cognitive impairment, OCD: obsessive compulsive disorder

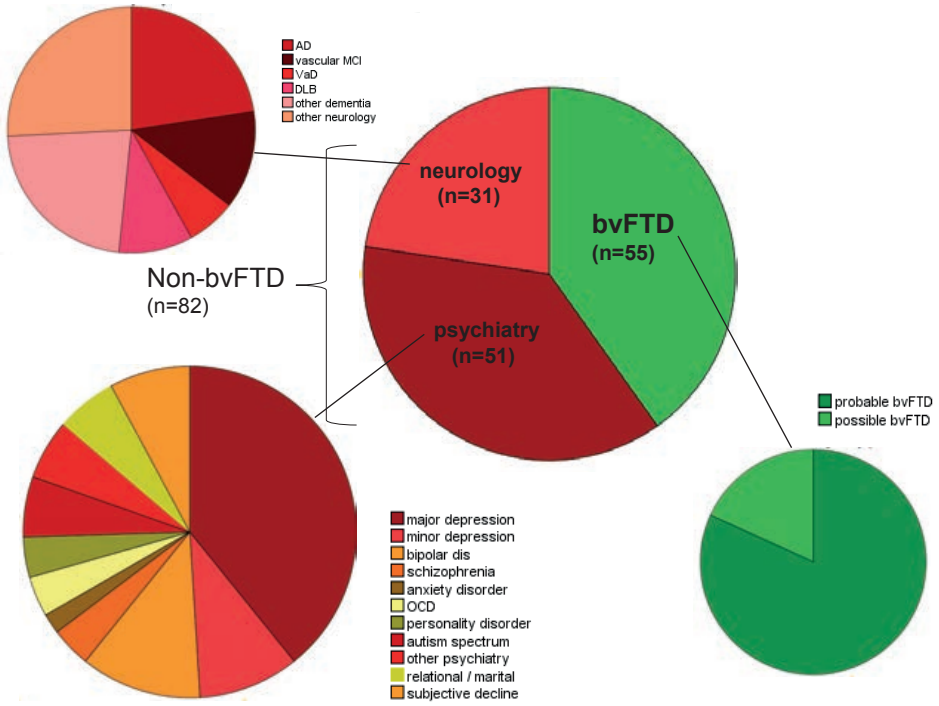

Figure 1: **Diagnoses underlying late onset frontal lobe syndrome**
n=137; pie charts representing different diagnoses underlying a LOF: bvFTD (40%), psychiatry (37%) and neurology (23%)

Demographics

The bvFTD and the non-bvFTD group did not differ in age (t(df=135)= -0.762, p=.440), gender (χ^2 (1, n=137)=2.81, p=.122), education (Mann-Whitney U=2058, p=.448) and disease duration (Mann-Whitney U=1928, p=.145) (Table 2).

Demographics	bvFTD (n=55)	non-bvFTD (n=82)	p-value
age (years, ± SD)	62.7 ± 6.5	61.9 ± 6.9	0.440 ╫
male gender, n (%)	63 (77%)	35 (64%)	0.122 □
education in years (median (IQR))	10.0 (9.0 – 14.0)	10.0 (10.0 – 14.0)	0.448 ⌂
years of disease duration (median (IQR))	3.0 (2.0 – 6.5)	3.0 (2.0 – 4.0)	0.145 ╔

Table 2: Demographics of the bvFTD and non-bvFTD groups (n=137)
Differences between groups were tested using ╫ t(df=135)=-0.762, p=.440), □ χ^2 (1, n=137)=2.81, p=0.122), ⌂U=2058, p=0.448, ╔ U=1928, p=0.145) . bvFTD: behavioral variant frontotemporal dementia, IQR: interquartile range.

Differentiating qualities of the screening instruments for bvFTD versus non-bvFTD

For none of the screening instruments a linear association with the diagnostic group was found, therefore they were categorized into quartiles. The logistic regression results for there quartiles of the MMSE, FAB, FBI and SRI are shown in Table 3.

MMSE and FAB

Logistic regression analyses showed that the MMSE (Wald = 1.87 , df=3, p=.60) and the FAB (Wald = 1.69, df=3, p=.64) could not differentiate between a bvFTD versus non-bvFTD diagnosis (see Table 3: Model 1 shows uncorrected values, Model 2 shows adjusted values for age and sex). The ROC curve for the MMSE and FAB are depicted in Figure 2. The MMSE had a poor differentiating quality with an AUC value of .61 (95% CI .52-.71). The FAB also had a poor differentiating quality with an AUC value of .62 (95% CI .52-.71) (Figure 2).

FBI

The FBI positive subscale (Appendix 1) could differentiate between bvFTD and non-bvFTD (Wald = 10.99, df=3, p=.01). A score above 12 (fourth quartile encompasses scores between 12 and 36) showed, compared to the reference category (first quartile, score below 5), an over five times increased risk for bvFTD diagnosis (OR 5.38, 95% CI 1.83-15.84, adjusted for age and sex) (Table 3).

The FBI negative subscale (Appendix 1) (Wald = 9.56, df=3, p=.02) showed a significantly increased risk for a bvFTD with increasing scores. Regression analyses of the separate quartiles revealed an increased bvFTD diagnosis risk for a score between 11 and 15 (second quartile) compared to the reference category (first quartile, score below 11) (OR 3.80, 95% CI 1.52-9.48) (Table 3).

The FBI positive subscale (FBI positive subscale taking into account age and sex, AUC .68, 95% CI .58-.77, Figure 2) and the FBI negative subscale (FBI negative subscale taking into account age and sex, AUC .67, 95% CI .58-.76, Figure 2) showed to have a slightly higher AUC, but still relatively poor quality for discriminating bvFTD from other LOF causes.

SRI

Logistic regression analysis of the total SRI (Appendix 2) score showed a discriminatory value for a bvFTD diagnosis versus a non-bvFTD diagnosis (Wald = 22.02, df=3 p=.000). A SRI score in the third (between 5 and 11) as well as in the fourth quartile (above 11, with a maximum possible score of 60) was associated with an increased risk of a bvFTD diagnosis (respectively, OR 4.25 (95% CI 1.45-12.45) and OR 9.94 (95% CI 3.33-29.71). These results remained unchanged before and after adjustment for age and sex (Table 3). As opposed to the other tests, the SRI turned out to have a fair distinguishing quality in differentiating bvFTD and non-bvFTD with an AUC of .73 (95% CI .64–.82, Figure 2).

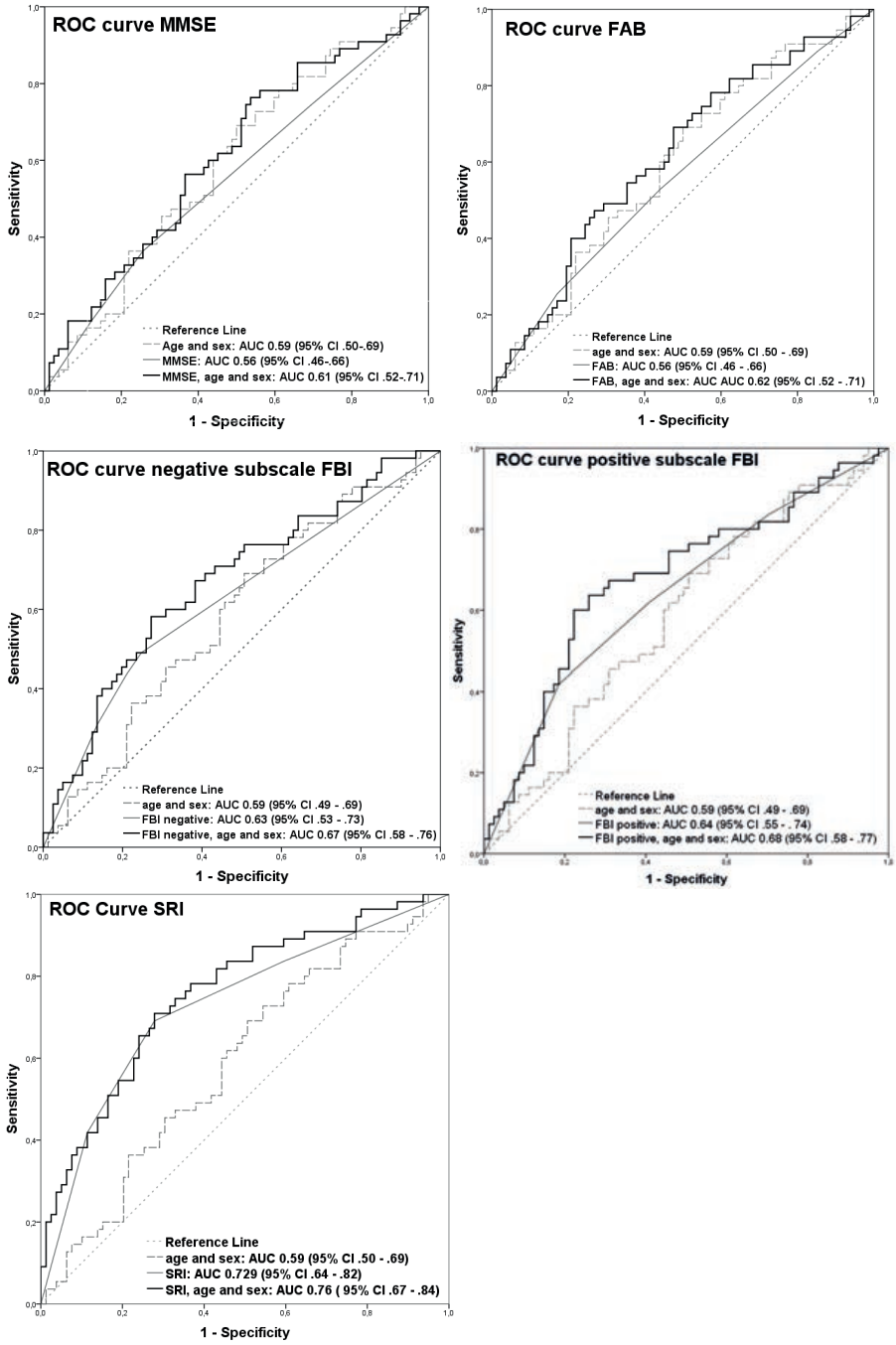

Figure 2: ROC curves for MMSE, FAB, FBI positive subscale, FBI negative subscale and SRI
n=137

	OR (95% CI)	OR (95% CI)
MMSE quartiles	**Model 1**	**Model 2**
MMSE (< 24)	Reference category	Reference category
MMSE (24 -26)	0.62 (0.21 – 1.81)	0.62 (0.21 – 1.93)
MMSE (27)	1.10 (0.32 – 3.75)	1.36 (0.38 – 4.85)
MMSE (28-30)	0.64 (0.23 – 1.76)	0.83 (0.28 – 2.41)
FAB quartiles	**Model 1**	**Model 2**
FAB (< 13)	Reference category	Reference category
FAB (14 -15)	1.47 (0.55 – 3.95)	1.58 (0.58 – 4.34)
FAB (16)	0.73 (0.23 – 2.49)	0.77 (0.23 – 2.61)
FAB (17-18)	0.86 (0.37 – 2.03)	0.92 (0.37 – 2.28)
FBI positive subscale quartiles	**Model 1**	**Model 2**
FBI positive (< 5)	Reference category	Reference category
FBI positive (5-7)	1.63 (0.56 – 4.76)	1.83 (0.60 – 5.53)
FBI positive (8-12)	1.33 (0.48 – 3.75)	1.53 (0.53 – 4.44)
FBI positive (12-36)	4.09 (1.50 – 11.17)*	5.38 (1.83 – 15.84)*
FBI negative subscale quartiles	**Model 1**	**Model 2**
FBI negative (< 11)	Reference category	Reference category
FBI negative (11-15)	3.37 (1.40 – 8.12)*	3.80 (1.52 – 9.48)*
FBI negative (16-19)	2.54 (0.78 – 8.26)	2.63 (0.80 – 8.75)
FBI negative (20-36)	2.18 (0.41 – 11.48)	2.53 (0.46 – 13.80)
SRI quartiles	**Model 1**	**Model 2**
SRI (0-1)	Reference category	Reference category
SRI (2-4)	1.14 (0.38 – 3.37)	1.25 (0.41 – 3.77)
SRI (5-11)	4.10 (1.44 – 11.70)*	4.25 (1.45 – 12.45)*
SRI (11-60)	9.09 (3.12 – 26.44)*	9.94 (3.32 – 29.71)*

Table 3: Logistic regression results for bvFTD: quartiles of MMSE, FAB, FBI and SRI (n=137)
Model 1: unadjusted data, Model 2: data adjusted for age and sex.
Significant results are marked with an *($p<0.05$). MMSE: mini-mental state examination, FAB: frontal assessment battery, FBI: frontal behavioral inventory, SRI: stereotypy rating inventory, OR: odds ratio.

Heterogeneity of the non-bvFTD group

To test if there were significant opposite effects between the neurological and the psychiatric patients (together creating the heterogeneous non-bvFTD group) that might mask a difference between one of these groups and the bvFTD-group, we repeated all analyses comparing the three major diagnostic groups (FTD, neurology and psychiatry): these analyses produced similar results (data not shown).

DISCUSSION

We assessed the prevalence of the broad spectrum of neuropsychiatric diagnoses underlying a late onset frontal lobe syndrome. The diagnoses were made multidisciplinary. Our results clearly illustrate the heterogeneous range of psychiatric and neurological (including neurodegenerative) causes. The most prevalent diagnosis was probable bvFTD. Nevertheless, the other types of dementia and alternative neurological diagnoses combined made out about a quarter as well. A third significant proportion of the subjects received a psychiatric diagnosis of which mood disorders make out the largest group. The fact that the same proportion (roughly one third) of subjects receives the diagnosis of probable bvFTD, another neurological diagnosis or a psychiatric diagnosis underlines the clinical dilemma in a LOF and confirms the suspected broad differential diagnosis. So far, the differentiating qualities of the examined inventories has only been examined within a group of mainly neurodegenerative disorders (e.g. AD, VaD) and healthy controls and information of their discriminating qualities within a neuropsychiatric cohort with similar frontal lobe features was lacking. The frequently used cognitive screening instruments MMSE and FAB performed poorly in predicting the major diagnostic outcome (both in the case of bvFTD versus non-bvFTD as well as in the case of three major diagnostic groups: bvFTD, other neurology and psychiatry). Thus these frequently used measurements of general cognition and frontal lobe function therefore do not contribute to the diagnostic process. Although the specifically developed assessment for frontal dysfunction, the FAB, has shown to differentiate FTD from AD, our results stress the importance of finding other instruments when bvFTD needs to be discerned from other frontal lobe syndrome causes [26].

The frontal behavior inventories (FBI, SRI) seemed to be more capable of discriminating bvFTD from other causes of a LOF. The scale specifically measuring apathy, loss of empathy, inflexibility and loss of insight (the negative subscale of the FBI) showed an increased risk for a bvFTD diagnosis, especially scores within the mid-range (score 11-15). The clinical relevance of this discriminating effect of these values is difficult to interpret since a FBI-score of 11 (positive and negative subscale added) was one of the possible inclusion criteria for the LOF-study. Furthermore, the higher values of the negative subscale of the FBI did not differentiate between bvFTD and non-bvFTD subjects. Possibly, a proportion of the psychiatric patients also received a relatively high negative subscale of the FBI score, because apathy is commonly reported in late-life depressive disorder [45]. We are therefore reluctant to suggest using the negative subscale of the FBI for differentiating bvFTD.

The scale specifically measuring disinhibition, restlessness, aggression and hyperorality (the positive subscale of the FBI) on the other hand, showed a stronger and clear relationship with a bvFTD diagnosis.

ROC curves showed that all tests, with exception of the SRI, had a poor discriminating accuracy as a test as a whole, even though specific scores within a certain quartile clearly

have discriminating qualities. This is clinically relevant since these instruments, especially the FAB and FBI, are advocated in the literature for identifying bvFTD [26;27;29;46;47]. A high total SRI score showed to be most indicative of a bvFTD diagnosis compared to a low total SRI score. The SRI therefore may very well have an added value in differentiating FTD from other LOF causes. The SRI seems to be a quite specific measure since stereotypy is typically absent in other LOF causes like AD, DLB or depression. Also, the number of patients with psychiatric diagnoses with clear stereotypical behavior, as theoretically could be seen in e.g. obsessive compulsive disorder, seems to be low in our cohort.

A strength of the present study is its naturalistic design, which make the results easily applicable for clinical practice. Another strength of this study is that the subjects were selected based on their symptoms instead of clinical diagnosis. However, this also presents a limitation, since a minimal score on the FBI and/or SRI was needed to fulfill inclusion criteria. Although the cut-off points of the FBI and SRI needed for inclusion are very low and although it is very rare for a subject to present with behavioral problems and not fulfill these inclusion cut-offs, theoretically it could cause selection bias, especially in significant results close to the inclusion cut-off (negative subscale FBI). This aside, our results strongly indicate that particularly the highest scores on these scales, which were far from the inclusion cut-offs, were indicative of a bvFTD diagnosis.

Another limitation of the present study is that patients in our tertiary referral center are relatively young and have relatively complex clinical features or atypical presentations. The results therefore cannot be easily generalized to any general neurodegenerative, memory of psychiatric clinic. However, a strength of the current approach is the recruitment of patients from both a memory clinic and an old age psychiatry department, thereby avoiding referral bias.

We are aware that neuropathological verification of the clinical diagnosis is not available for our cohort. We used the multidisciplinary consensus diagnosis based on extensive clinical and biomarker evaluation as the 'silver standard'. Nonetheless, we can not exclude that in a small minority of cases with a psychiatric diagnosis an underlying neurodegenerative disorder was missed [48]. Re-evaluation of the clinical diagnosis after follow-up, including the development of co-morbid disorders will shed more light on this issue.

Since neurodegenerative disorders are progressive and eventually mortal, while for psychiatric disorders usually treatment is available, the differentiation between bvFTD and psychiatric diagnoses or other neurological causes is very relevant. It holds consequences for patients' care management. Especially in the light of future neurodegenerative disease modifying therapies, this differentiation is gaining even more importance. Since the commonly used cognitive screening methods in this study showed a low capability in predicting the diagnostic outcome we would recommend future examination of more detailed clinical behavioral features or cognitive measures. To date, none of these screening instruments can approximate the differentiating quality of a profound clinical workup

combined with imaging and biomarker examination. The added value of these imaging techniques and CSF biomarkers in the early diagnostic process of a LOF needs to be prospectively examined.

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