## The frontal lobe syndrome

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Chapter 8

# THE PITFALL OF BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA MIMICS DESPITE MULTIDISCIPLINARY APPLICATION OF THE FTDC CRITERIA

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## ABSTRACT

**Background:** The behavioral variant of frontotemporal dementia (bvFTD) has a broad differential diagnosis including other neurological and psychiatric disorders. Psychiatric misdiagnoses occur in up to 50% of bvFTD patients. Numbers on misdiagnosis of bvFTD in psychiatric disorders are lacking.

**Objective:** The aim of our study was to investigate the frequency and characteristics of bvFTD misdiagnoses in psychiatric disorders and other neurologic disorders.

**Methods:** Thirty-five patients with a (*possible* or *probable*) bvFTD diagnosis made by a specialized memory clinic neurologist were included. Change in diagnosis after consulting a psychiatrist at baseline was recorded as well as change in diagnosis after two years of multidisciplinary neuropsychiatric follow-up. Differences in cognitive and behavioral profiles were investigated per diagnostic group after follow-up (bvFTD, psychiatry, other neurologic disorders).
Clinical profiles of the patients are described in detail.

**Results:** In 16 patients (45.5%) the bvFTD baseline diagnosis changed: 2 at baseline after psychiatric consultation and 14 after two years of multidisciplinary follow-up. A majority of 10 (62.5%) of these 16 patients (28.5% of total) were reclassified with a psychiatric diagnosis. We found no differences for cognitive and behavioral baseline profiles between patients with bvFTD versus psychiatric diagnoses.

**Conclusion:** In almost half of the initial bvFTD cases, diagnosis was changed after follow-up, most often into a psychiatric disorder. A multidisciplinary neuropsychiatric approach in the diagnostic process of bvFTD results in the identification of treatable disorders that otherwise would have been missed. Our findings suggest a limited specificity and a limited positive predictive value of the bvFTD criteria.

## INTRODUCTION

Behavioral variant frontotemporal dementia (bvFTD) is characterized by a frontal lobe syndrome, resulting in profound behavioral and character changes, caused by a neurodegenerative disease [1;2]. However, many diseases of neurologic as well as psychiatric origin, may show a similar frontal lobe syndrome as seen in bvFTD [3-7]. Fortunately, recent research has made great progress in improving diagnostic biomarkers for the main neurodegenerative differential diagnoses (Alzheimer's disease (AD), Dementia with Lewy Bodies (DLB) and vascular dementia (VaD)), discriminating them more easily from bvFTD [8-12]. Nowadays, the main clinical dilemma is formed by the psychiatric differential diagnosis of bvFTD [6;13;14]. Differentiating between early bvFTD and primary psychiatric disorders is challenging due to the lack of a disease-specific biomarker, the absence of insight of the patients and the fact that bvFTD may present with psychiatric symptoms, fitting psychotic, compulsive or mood disorders [14]. Typical features like apathy, loss of initiative and economy of speech are seen in bvFTD as well as in negative symptoms in schizophrenia or mood disorders [15-23]. Similarly, in bipolar disorder, anxiety disorders, obsessive-compulsive disorder, autism or tic syndromes other behavioral disturbances like stereotypical or compulsive language and behavior or disinhibition occur as seen in bvFTD [24-27]. Especially in the bvFTD subgroup with a C9orf72 mutation, psychiatric symptoms are often the presenting feature and a disease duration up to 20 years has been described, complicating differentiation from primary psychiatric causes [6;14;28;29]. As a consequence, up to 50% of bvFTD patients initially receives a psychiatric misdiagnosis [13]. Not much is known about misdiagnosis the other way around: bvFTD misdiagnosis in psychiatric disorders. With the publication of the Frontotemporal Dementia Consortium bvFTD criteria sensitivity has clearly improved, but specificity for bvFTD within a patient group with early manifestation of frontal lobe symptomatology, including psychiatric disorders, is unknown and might be limited [30]. The number of psychiatric patients fitting a bvFTD diagnosis according to the FTDC criteria has not been prospectively examined before. Since bvFTD is progressive and will eventually lead to death, whereas psychiatric disorders are treatable, every approach adding to the correct discrimination between the two is of paramount importance [14;31]. Our aim was to prospectively investigate the number of bvFTD misdiagnoses in other diagnoses, including primary psychiatric disorders, when applying the FTDC criteria in a memory clinic setting. Secondly, our aim was to examine whether the baseline characteristics differed between the patient group with a stable bvFTD diagnosis over time and the groups in which diagnosis was changed towards either a psychiatric diagnosis or a neurologic disorder. Especially characterizing the subgroup of patients with a psychiatric disorder mimicking bvFTD is of interest, since these patients are at risk for serious treatment delay.

## METHODS

### Participants

Study subjects were participants of the LOF-study (Late Onset Frontal lobe syndrome study, inclusion between April 2011 and June 2013), an observational prospective follow-up study including 137 subjects aged 45-75 years of which the study design and baseline characteristics were published previously [7;32]. The LOF study was designed to investigate which factors contribute to an early and accurate bvFTD diagnosis in a neuropsychiatric cohort. This present study focused on a subgroup with potential bvFTD misdiagnosis. For the present study subjects were drawn from the LOF-study when they had been referred to the memory clinic of the Alzheimer center (VU University Medical Center), were diagnosed with *possible* or *probable* bvFTD by a specialized neurologist after a standardized assessment and a follow-up diagnosis after two years was available. Patient who died during follow-up, were only included when there was no doubt on the underlying disease remained at the time of death.

### Diagnostic assessment

All patients underwent standardized clinical assessment, consisting of behavioral and cognitive medical history, neurological exam, Mini-Mental State Examination (MMSE), frontal assessment battery (FAB), Montgomery-Asberg Depression Rating Scale (MADRS), Positive And Negative Symptom Scale (PANSS), and a neuropsychological test battery [32]. Informant based behavioral screening instruments were used to assess behavioral disturbances: the Frontal Behavioral Inventory (FBI), which is split in a positive (disinhibition) and a negative subscale (apathy and inertia), and the Stereotypy Rating Inventory (SRI).

All patients underwent an MRI-scan of the brain, visually assessed using the appropriate scales [33-35]. In case of normal MRI findings or doubt on the interpretation of the abnormalities being explanatory for the behavioral changes an [$^{18}$F]FDG-PET-scan was made. CSF was obtained with a lumbar puncture, performed according to 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. Reasons for not obtaining CSF included technical difficulties, use of oral anticoagulants, and patient refusal.

After clinical assessment a specialized neurologist (Y.P., N.P., P.S.) determined the most likely baseline diagnosis taking into account results from neuropsychological assessment, neuroimaging and CSF. A specialized psychiatrist (A.D, C.K., M.S.) also determined the most likely diagnosis at baseline, independent of the neurologist, taking into account all the available test results. In a subsequently held multidisciplinary meeting the neurologist could revise the diagnosis into the most likely baseline diagnosis after consulting the psychiatrist. Diagnoses were based upon the total workup described above and 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, the DSM-IV for psychiatric disorders and the FTDC criteria for bvFTD [10;12;30;36].

This preliminary multidisciplinary diagnosis with the highest evidential ground possible at baseline was used as a clinical diagnosis in order to treat and guide the patient and caregivers. Patients were regularly followed in a clinical multidisciplinary setting.
After 2 years of follow-up the clinical diagnosis was re-evaluated based on the clinical course, repeated MRI and repeated neuropsychological examination. For each patient a multidisciplinary meeting was held in which all available factors were carefully weighed. The final diagnosis after two years of follow-up was used as a gold standard.

For analysis the patients were grouped into ' bvFTD', 'psychiatry' and 'other neurological disorders' based on their multidisciplinary follow-up diagnosis. In order to characterize the subjects in more detail a subdivision in *possible* and *probable* bvFTD was made. In case of a positive family history for dementia, patients were referred for clinical genetic counseling and optional genetic screening for MAPT, GRN, PSEN1 and APP genes. Taking into account the clinical overlap in C9orf72 cases and psychiatric disorders, C9orf72 genotyping was performed in all cases as part of this study [6;14;28;29].

**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 University medical center Amsterdam, the Netherlands. All subjects gave written informed consent for the use of their clinical data for research purposes.

**Statistical analysis**

Statistical analyses were performed using the IBM SPSS Statistics for Windows, version 22. Demographic baseline characteristics were compared between diagnostic patient groups (bvFTD diagnosis, psychiatric diagnosis or other neurological diagnoses (OND). Dichotomous variables were compared using the Pearson's $\chi^2$ test. Non-parametric tests were used to investigate relationships between the diagnostic groups and the clinical scales (FBI, SRI, MMSE and FAB) because of the small sample size (Kruskal-Wallis). For significant findings, posthoc analyses were performed using Mann-Whitney U test with Bonferroni correction for multiple comparison. Results were considered to be statistically significant if $p < 0.05$ unless otherwise indicated.

## RESULTS

A total of 35 patients received a *possible* bvFTD (n=5) or a *probable* bvFTD (n=30) diagnosis by the memory clinic neurologist at baseline and had follow-up information available. In 16 (45.5%) of the 35 patients, the bvFTD baseline diagnosis was changed. In two patients, the diagnosis was changed at baseline after psychiatric consultation and in 14 patients diagnosis was changed after two years of multidisciplinary follow-up by the neurologist and psychiatrist (Table 1). Ten patients (62.5% of the patients with a changed diagnosis, 28.5% of the total) eventually received a psychiatric diagnosis, of which mood disorders were the most common. Six patients (17%) received other neurologic diagnoses (OND), most commonly other neurodegenerative disorders like semantic dementia. The remaining 19 patients had a *probable* bvFTD diagnosis after two years based on the FTDC consensus criteria [30]. In all 5 cases with an initial *possible* bvFTD diagnosis made by the neurologist at baseline, the diagnosis changed towards a psychiatric diagnosis.

| **Patients diagnosed with bvFTD by neurologist at baseline, n=35** | **bvFTD** | **Psychiatric diagnosis** | **OND** |
|---|---|---|---|
| Baseline diagnosis neurologist and psychiatrist (% of total group) | 33 (94.5%) | 2 (5.5%) | 0 (0%) |
| Follow-up diagnosis neurologist and psychiatrist (% of total group) | 19 (54.5%) | 10 (28.5%) | 6 (17%) |

**Table 1: Diagnosis after consultation psychiatrist at baseline and after two years multidisciplinary follow-up**

bvFTD: behavioral variant frontotemporal dementia, OND: other neurologic disease.

No significant differences were found for age of onset (Kruskal-Wallis: H(2)=.07, p=.97), sex (Pearson's $\chi^2$ (2) = 3.15, p=.21) and education (H(2)=.06, p=.97) between the three final diagnostic groups (stable bvFTD: 'FTD', changed to psychiatry: 'psychiatry' and changed to other neurologic disorders: 'OND') (Table 2) after multidisciplinary follow-up.

| | **bvFTD (n=19)** | **Psychiatry (n=10)** | **OND (n=6)** | **p-value** |
|---|---|---|---|---|
| **Age of onset** (years) median (IQR) | 58 (52-65) | 60 (54-62) | 56 (55-62) | 0.97 ╥ |
| **Sex** (males (% within diagnosis)) | 11 (58%) | 9 (90%) | 4 (66.5%) | 0.21 † |
| **Education** (years) median (IQR) | 10 (10-14) | 11 (9-15) | 11 (10-15) | 0.97 ╥ |

**Table 2: Demographics for diagnostic groups**

bvFTD: behavioral variant frontotemporal dementia, OND: other neurologic disease. IQR: interquartile range, 25th – 75th percentile. ╥ Kruskal-Wallis, † Pearson's $\chi^2$

Group differences between the three diagnostic groups after follow-up (bvFTD, psychiatric diagnoses and OND) were examined for the baseline results of the cognitive screening instruments and informant-based behavioral questionnaires. Results are depicted in Figure 1. No significant differences were found for the MMSE (Kruskal-Wallis: H(2)=.20, p=.91), FAB (Kruskal-Wallis: H(2)=2.74, p=.26), positive subscale of the FBI (Kruskal-Wallis: H(2)=3.53, p=.17) and the negative subscale of the FBI (Kruskal-Wallis: H(2)=0.25, p=.88) (Figure 1).

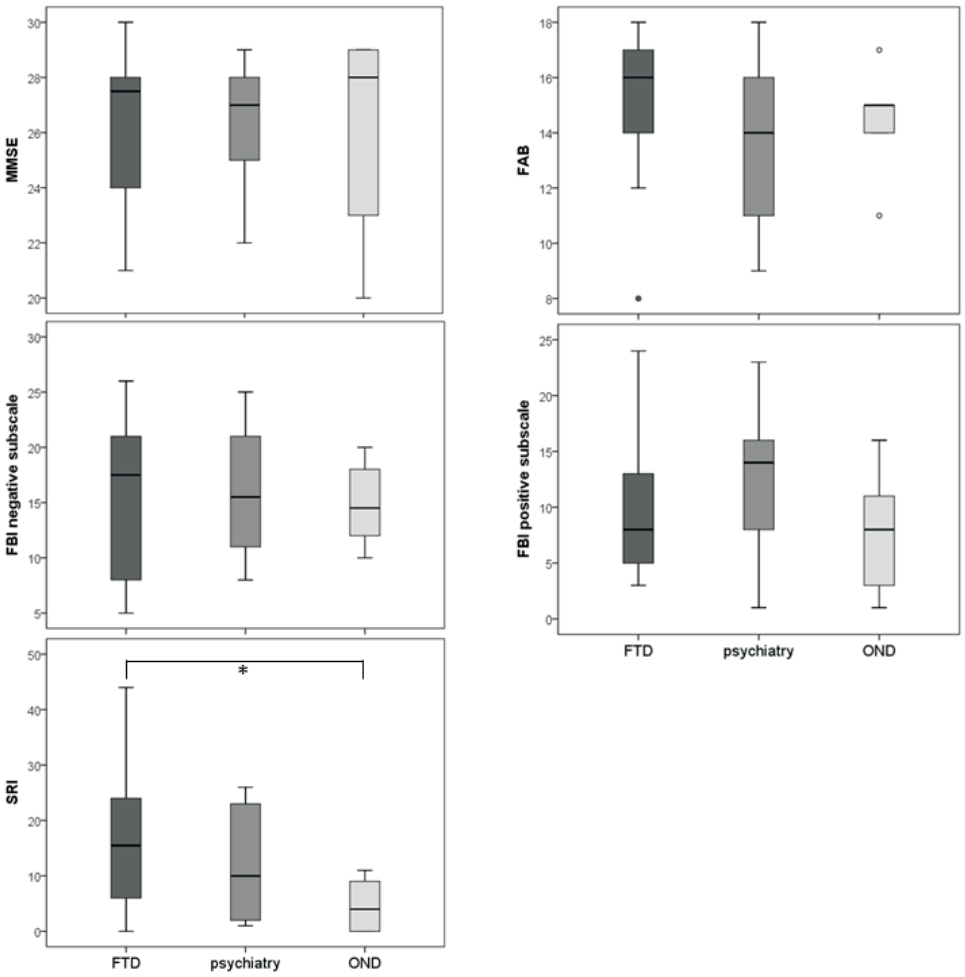


**Figure 1: Box and whisker plots for MMSE, FAB, FBI and SRI for diagnostic groups**
Significant differences are marked with an asterix*. FTD: frontotemporal dementia (dark grey), OND: other neurologic disorder (light grey). MMSE: mini mental state examination, FAB: frontal assessment battery, FBI: frontal behavioural inventory, SRI: stereotypy rating inventory.

For the SRI, a significant group difference was found (Kruskal-Wallis: $H(2)=6.41$, $p=.04$) (Figure 1). Post-hoc analyses (with a Bonferroni corrected significance level of $p<0.02$) showed a significant higher score on the SRI in bvFTD patients compared to OND patients (Mann-Whitney $U(1)=20.50$, $p=0.02$). The other diagnostic groups did not differ significantly (FTD vs psychiatry: $p=.25$, psychiatry vs OND: $p=.09$) (Figure 1).

Table 3 shows the clinical descriptive characteristics of the patients and the clinical disease courses during follow-up. In most cases the clinical course of the disease and the evolution of symptoms combined with the presence or absence of neuroimaging progression, was very relevant for the final follow-up diagnosis. The patients in which the diagnosis was changed from bvFTD into a psychiatric diagnosis, complained about impaired memory function most frequently at baseline (n=7) or had no complaint at all (n=5), while their spouse or informant complained about more behavioral issues (Table 3). Part of these patients did not officially fulfill the criteria for a major psychiatric diagnosis. For instance, in these patients subthreshold mood disorders combined with impaired coping strategies due to personality (disorder) traits or severe relational disputes were found. Although some improvement was seen on the cognitive and behavioral screening instruments, in many of these patients the scores fluctuated or remained stable (two patients refused part of the follow-up assessment). The patients in which a probable bvFTD diagnosis was maintained almost all showed clear clinical progression, including the development of severe behavioral problems, the development of motor neuron disease in three patients, nursing home admission in four cases, prosopagnosia in one case and aphasia or semantic deficits in six patients (Table 3). Almost half of the bvFTD patients were unable to complete the follow-up assessment due to serious disease progression. In one patient a progranulin mutation was found and in one patient a C9orf72 repeat expansion was found (Table 3, case number 17 and number 35). In these two patients their final diagnosis was changed from *probable* bvFTD into *definite* bvFTD. All other subjects tested negative for C9orf72 mutation screening. More details on clinical reasoning and neuroimaging findings on an individual patient level are given in Table 3.

| Patient (M/F) | age | Diagnosis T2 | D | FBI T0 | FBI T2 | SRI T0 | SRI T2 | MMSE T0 | MMSE T2 | FAB T0 | FAB T2 | Imaging | Clinical course T0-T2 . Bold symptoms: main complaint of informant |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 M | 46 | **major depression*** | 5 | 20 | 12 | 23 | 6 | 27 | 29 | 16 | 16 | T0 MRI: n.a. T0 *FDG: fitting FTD* T2 MRI: no progression | Hypochondriac delusions, somatic complaints e.c.i., **obsessive behavior**. Anxiety and depression became more and more apparent during FU; almost full recovery after ECT, besides mild remaining anxiety and some lack of initiative. |
| 2 F | 58 | **major depression*** | 3 | 42 | m | 26 | m | 24 | m | 14 | m | T0: MRI: n.a. *T0 FDG: fitting FTD* T2: m (refusal due to anxiety) | **Social withdrawal, severe emotional indifference,** apathy, anhedonia, restlessness and eating rituals**.** Admission old age psychiatry ward for diagnostic observation: symptoms due to anxiety, depression and anorexia nervosa (late onset). So far no effects medication and ECT. |
| 3 M | 56 | **bipolar disorder*** | 3 | 19 | 20 | 2 | 1 | 28 | 30 | 17 | 17 | T0 MRI: n.a. T0 FDG: n.a. T2 MRI: no progression, n.a. | **Disinhibition**, euphoria and social inappropriate behavior. Patient complaint: memory impairment. Conclusion: symptoms due to bipolar disorder. Mood stabilized after treatment during FU, other frontal behavioral symptoms stayed stable. |
| 4 M | 66 | **exacerbation personality disorder*** | 1 | 32 | 37 | 12 | 7 | 27 | 24 | 11 | 15 | T0 MRI: n.a. *T0 FDG: fitting FTD* T2 MRI: no progression, n.a | Irritability, **emotional indifference**, mental rigidity and somatic complaints (e.c.i.). Due to combination of cluster C personality disorder and mild depressive symptoms. No progression. Treatment started recently; mental flexibility improved with medication. |
| 5 M | 62 | **minor depression, impulse control disorder*** | 4 | 27 | 22 | 1 | 3 | 27 | 26 | 16 | 16 | T0 MRI: n.a. T0 FDG: n.a. T2 MRI: no progression, n.a | Irritability and **aggression**, **disinhibition**, loss of empathy and initiative. Due to minor depression with impulse control problems; may be partly induced by sleep deprivation due to obstructive sleep apnea syndrome. No clinical progression over time during FU. |

| Patient (M/F) | age | Diagnosis T2 | D | FBI T0 | FBI T2 | SRI T0 | SRI T2 | MMSE T0 | MMSE T2 | FAB T0 | FAB T2 | Imaging | Clinical course T0-T2 . Bold symptoms: main complaint of informant |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 M | 59 | **exacerbation personality disorder, relational problems*** | 1 | 47 | 44 | 2 | 6 | 22 | 29 | 12 | 17 | T0 MRI: n.a. *T0 FDG: fitting AD*** T2 MRI: no progression, n.a | Increasing discrepancy between clinical observations (improved insight in behavior and less irritability during follow up) and information given by spouse (increasingly severe behavioral disturbances, **aggression**, **obsessive behavior**) in a patient with cluster C personality disorder. |
| 7 M | 44 | **exacerbation personality disorder*** | 7 | 36 | 30 | 24 | 0 | 28 | 21 | 12 | 14 | T0 MRI: n.a. T0 FDG: n.a. T2 MRI: no progression, n.a | Increasing discrepancy between clinical observation (stable or subtle improvement of irritability and jocularity) and information given by spouse (increasingly severe behavioral disturbances, **loud inappropriate and childish behavior,** hyperorality) in a patient with cluster B personality disorder. Patient only complained of memory impairment. |
| 8 M | 60 | **minor depression and relational problems*** | 1 | 41 | m | 10 | m | 27 | m | 10 | m | T0 MRI: n.a. *T0 FDG: fitting FTD* T2 MRI: m (refused) | Loss of empathy, aggression, **apathy** and hyperorality; during FU increasing insight in own behavior and relational dispute became apparent. Patient increasingly expressed depressive symptoms. Mild improvement after pharmacological treatment. |
| 9 M | 62 | **severe relational problems / marital dispute*** | 1 | 11 | 19 | 1 | 11 | 29 | 30 | 14 | 17 | T0 MRI: nonspecific neurodegenerative features *T0 FDG: fitting FTD* T2 MRI: slight progression non-specific features | **Emotional indifference**, loss of decorum and mild cognitive impairments. Stable course and some minor improvement of cognitive test results. Patient complained of memory impairment. |

| Patient (M/F) | age | Diagnosis T2 | D | FBI T0 | FBI T2 | SRI T0 | SRI T2 | MMSE T0 | MMSE T2 | FAB T0 | FAB T2 | Imaging | Clinical course T0-T2 . Bold symptoms: main complaint of informant |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 M | 61 | **severe relational problems / marital dispute*** | 2 | 21 | 0^ | 10 | 0^ | 25 | 27 | 18 | 18 | T0 MRI: n.a. T0 FDG: n.a. T2 MRI: no progression, n.a. | Apparent loss of initiative, **disinhibition and rude behavior**. During FU this seemed to be mostly based on severe marital dispute. Clear improvement of mood and behavior after divorce. Patient had no complaints. ^ the T2 FBI and SRI are with a different informant (daughter) after divorce (T0 with spouse at the time). |
| 11 M | 60 | **semantic dementia †** | 4 | 23 | 20 | 8 | 4 | 29 | m | 17 | m | T0 MRI: n.a. *T0 FDG: fitting FTD* T2 MRI: some progression global atrophy | Emotional indifference and **irritability**. Patient only complained of impaired memory function. During FU progressive semantic impairments. Disease insight and awareness declined during FU. |
| 12 F | 67 | **semantic dementia †** | 2 | 13 | 10 | 0 | 0 | 23 | m | 11 | m | T0 MRI: non-specific neurodegeneration *T0 FDG: fitting FTD* T2 MRI: m | Subtle **loss of initiative**, **apathy** and minor fluency problems at inclusion. Patients had no complaints. During follow-up word finding difficulties and increasing deficiency of semantic knowledge; behavioral problems less pronounced. |
| 13 M | 56 | **cortical basal syndrome †** | 3 | 26 | 34 | 9 | 0 | 28 | 25 | 15 | 10 | T0 MRI: n.a. *T0 FDG: fitting FTD* T2 MRI: mild progression of right sided diffuse atrophy | **Inflexibility**, inappropriate laughter and jocularity. Patient had no complaints, except fatigue. During FU patient developed compulsive behavior, bradykinesia and apraxia. |
| 14 F | 53 | **postanoxic encephalopathy†** | 3 | 36 | 38 | 11 | 19 | 20 | m | 15 | m | T0 MRI: n.a. *T0 FDG: fitting FTD* T2 MRI: some mesiofrontal atrophy, fitting normal aging | Cognitive impairments, **apathy**, hyperorality and perseveration . Patient had no complaints. No progression during follow up, in retrospect probably postanoxic damage during surgery; patient did develop some depressive symptoms during follow up which responded well to medication. |

| Patient (M/F) | age | Diagnosis T2 | D | FBI T0 | FBI T2 | SRI T0 | SRI T2 | MMSE T0 | MMSE T2 | FAB T0 | FAB T2 | Imaging | Clinical course T0-T2 . Bold symptoms: main complaint of informant |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 M | 56 | **multiple sclerosis†** | 1 | 25 | 13 | 0 | 7 | 28 | m | 14 | m | T0 MRI: fitting multiple sclerosis *T0 FDG: fitting FTD or PSP* T2 MRI: no progression | **Emotional indifference,** irritability and bradyphrenia. Increasingly mistakes in administration and at work. Patient had no complaints except some mild memory complaints. Clinical progression during follow-up. |
| 16 M | 56 | **Parkinson's disease dementia †** | 10 | 15 | 35 | 0 | 6 | 29 | 26 | 15 | 15 | *T0 MRI: fitting FTD* T2 MRI: m | **Disinhibition, hyperorality,** inappropriate behavior and mental inflexibility**.** Patient complained of impaired memory function. Slight tremor of the right hand. During FU clear hypokinetic rigid syndrome, followed by increasing cognitive disorders. |
| 17 F | 58 | **bvFTD** | 3 | 11 | 25 | 0 | 1 | 26 | 15 | 16 | 4 | T0 MRI: *T0 PET: fitting FTD and/or AD* T2 MRI: Severe progression of (right sided) frontal atrophy | **Loss of initiative** and memory impairment. Clinical behavioral progression during FU with stereotypical and compulsive shopping behavior. Referral to clinical genetics followed: progranulin-mutation was found (final diagnosis: *definite* bvFTD). |
| 18 F | | **bvFTD** | 5 | 30 | 34 | 26 | 21 | 24 | 29 | 18 | 18 | *T0 MRI: fitting (right > left) FTD* T2 MRI: Progression of atrophy fitting FTD | **Disinhibition,** hyperorality and impulsive/ dangerous behavior. Patient had no complaints. Clinical behavioral progression with aggression, compulsive behavior and increased religious interest. During FU economy of speech and semantic deficits, nursing home admission followed. |
| 19 M | | **bvFTD** | 2 | 25 | 43 | 11 | 20 | 26 | 0 | 0 | 0 | T0 MRI: fitting FTD and /or AD *T0 PET: fitting FTD* T2 MRI: m | **Disinhibition, obsessive behavior** and loss of empathy. During FU clear clinical behavioral progression was seen, combined with a progressive aphasia, semantic deficits and mild parkinsonism. |

| Patient (M/F) | age | Diagnosis T2 | D | FBI T0 | FBI T2 | SRI T0 | SRI T2 | MMSE T0 | MMSE T2 | FAB T0 | FAB T2 | Imaging | Clinical course T0-T2 . Bold symptoms: main complaint of informant |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 M | | **bvFTD** | 6 | 29 | 34 | 44 | 10 | 29 | 25 | 14 | 13 | *T0 MRI: endstage frontotemporal atrophy* T2 MRI: endstage frontotemporal atrophy | **Stereotypical and obsessive behavior**, increased religious interests, inappropriate behavior and mental rigidity. Patients had no complaints. Clear clinical behavioral progression during FU progressive semantic impairment. |
| 21 F | | **bvFTD** | 8 | 13 | 21 | 11 | 16 | 27 | 15 | 27 | 15 | *T0 MRI: fitting AD* ** T2 MRI: progression of non-specific atrophy | Slowly progressive **irritability**, obsessive shopping behavior. Patient has slight memory complaints. During FU severe disinhibition and other forms of clinical behavioral progression with memory impairment. |
| 22 M | | **bvFTD** | 7 | 35 | 31 | 21 | 16 | 30 | 21 | 13 | 14 | *T0 MRI: fitting FTD and/ or AD*** *T0 PET: fitting FTD* T2 MRI: Progression of atrophy | **Social withdrawal, mental rigidity**, diminished self-care and echolalia. Clear clinical progression during FU with palilalia and eventually day-care at nursing home facility was organized. |
| 23 M | | **bvFTD** | 4 | 13 | 19 | 4 | 9 | 28 | m | 16 | m | *T0 MRI: fitting FTD* T2 MRI: m | Irritability, **aggression and prosopagnosia**. Clinical behavioral progression with memory impairment and increasing loss of empathy. |
| 24 M | | **bvFTD** | 2 | 26 | m | 16 | m | 30 | m | 15 | m | *T0 MRI: fitting FTD* *T0 PET: fitting FTD* T2 MRI: m | **Loss of empathy**, loss of initiative, **obsessive behavior** and anxiety. Clinical behavioral progression with severe aphasia, repetitive behavior and nursing home admission during FU. |
| 25 F | | **bvFTD** | 1 | 25 | m | 2 | m | 24 | m | 8 | m | *T0 MRI: fitting FTD* T2 MRI: m | Economy of speech, echopraxia and **stereotypical behavior**. Patient had complaints of memory impairment. Clinical behavioral progression during FU, as well as severe aphasia. Patient developed MND /ALS. Deceased during FU. |

| Patient (M/F) | age | Diagnosis T2 | D | FBI T0 | FBI T2 | SRI T0 | SRI T2 | MMSE T0 | MMSE T2 | FAB T0 | FAB T2 | Imaging | Clinical course T0-T2 . Bold symptoms: main complaint of informant |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 26 M | | **bvFTD** | 2 | 26 | m | 26 | m | 22 | m | 16 | m | T0 MRI: non-specific neurodegenerative features *T0 PET: fitting FTD* T2 MRI: Progression of atrophy | Stereotypical and **compulsive** behavior, **disinhibited** when with strangers, apathy at home. Patient has no complaints. Clinical behavioral progression during FU, as well as severe aphasia. Patient developed MND /ALS. Deceased during FU. |
| 27 M | | **bvFTD** | 4 | 9 | 12 | 19 | 6 | 28 | 29 | 17 | 18 | *T0 MRI: fitting FTD or AD* ** T2 MRI: no progression | **Loss of empathy, social withdrawal** and mild stereotypical behavior. Clinical behavioral progression and patient developed prosopagnosia and increasing motor tics. |
| 28 F | | **bvFTD** | 3 | 37 | 56 | 37 | 27 | 22 | m | 18 | m | *T0 MRI: fitting FTD* T2 MRI: Progression of atrophy | Loss of empathy**, irritability**, emotional bluntness and subtle **motor tics**. Clinical behavioral progression during FU, with severe stereotypical motor behavior, obsessive behavior and perseveration. Admission in nursing home followed. |
| 29 F | | **bvFTD** | 11 | 28 | m | 17 | m | 29 | m | 17 | m | *T0 MRI: fitting FTD* T2 MRI: m | **Hypochondria, compulsive behavior**, loss of empathy and loss of interest in others. Clinical behavioral progression with aggression and hyperorality, aprosodia, economy of speech and language impairments leading to complete aphasia during FU. |
| 30 F | | **bvFTD** | 2 | 22 | m | 3 | m | 28 | m | 18 | m | *T0 MRI: fitting FTD* T2 MRI: m | Loss of empathy, **egocentric** behavior and emotional bluntness. Clinical behavioral progression during FU with disinhibited and compulsive behavior. Patient developed MND / ALS. Deceased during FU. |

| Patient (M/F) | age | Diagnosis T2 | D | FBI T0 | FBI T2 | SRI T0 | SRI T2 | MMSE T0 | MMSE T2 | FAB T0 | FAB T2 | Imaging | Clinical course T0-T2 . Bold symptoms: main complaint of informant |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 31 M | | **bvFTD** | 3 | 35 | m | 15 | m | 28 | m | 15 | m | T0 MRI: n.a. *T0 PET: fitting FTD* T2 MRI: m | **Mental rigidity**, loss of empathy and hyperorality. Patient complained of memory impairment. Clinical behavioral progression during FU with echolalia and eventually aphasia. Patient developed MND / ALS during FU. |
| 32 F | | **bvFTD** | 4 | 50 | m | 24 | m | 24 | m | 17 | m | *T0 MRI: fitting FTD* T2 MRI: m | Loss of empathy, loss of interest and stereotypical motor behavior. Patients complained of memory impairment. Clinical behavioral progression with severe apathy, disinhibition and mental rigidity. Admission in nursing home during FU. |
| 33 M | | **bvFTD** | 4 | 37 | 34 | 14 | 42 | 28 | 18 | 12 | 0 | *T0 MRI: fitting FTD* T2 MRI: m | Loss of interest**, irritability** and **hoarding** with shop lifting. Patient had no complaints. Clinical behavioral progression with aggression, mental rigidity and semantic impairment. Admission in nursing home followed during FU. |
| 34 F | | **bvFTD** | 4 | 12 | m | 6 | m | 21 | m | 18 | m | *T0 MRI: fitting FTD* T2 MRI: m | **Emotional bluntness** and apathy. Patient expressed somatic complaints. Clinical behavioral progression with disinhibition and prosopagnosia during FU. Admission in nursing home followed during FU. |
| 35 M | 46 | **bvFTD** | 4 | 14 | 10 | 7 | 2 | 24 | 24 | 14 | 14 | T0 MRI: non-specific features fitting neurodegeneration *T0 FDG: fitting FTD* T2 MRI: no progression | L**oss of initiative**, **loss of empathy**, apathy, psychotic features and cognitive impairments during FU. Patient had no complaints. C9orf72 repeat expansion found (final diagnosis: *definite* bvFTD). |
| **patient** | **age** | **Diagnosis T2** | **D** | **FBI T0** | **FBI T2** | **SRI T0** | **SRI T2** | **MMSE T0** | **MMSE T2** | **FAB T0** | **FAB T2** | **Imaging** | **Clinical course T0-T2** |

## DISCUSSION

Almost half of the bvFTD diagnoses made by the specialized memory clinic neurologist with the use of the FTDC criteria at baseline were changed, either after psychiatric consultation or after multidisciplinary neuropsychiatric follow-up. The most striking finding in this study is the number of bvFTD baseline misdiagnoses in actual psychiatric patients, since these patients have a curable or at least treatable disease. Especially a *possible* bvFTD diagnosis should be applied with caution and followed up carefully, since in our cohort all *possible* bvFTD baseline diagnoses were withdrawn during follow-up. We found six patients with other neurological disorders responsible for the behavioral disturbances initially labeled as bvFTD. Since the majority of these subjects had other neurodegenerative disorders, partly considered to be part of the same neurodegenerative spectrum (e.g. semantic dementia, corticobasal syndrome), these findings have less clinical impact because these patients are receiving proper and adequate memory clinic care from baseline on, even though their diagnosis changed during follow-up. However, patients with a psychiatric disorder would have missed adequate referral and treatment and their prognosis might have been worsened by diagnostic delay, had they not received clinical follow-up by a psychiatrist.

The recently developed FTDC criteria signify a great step forward, incorporating neuroimaging to determine the level of diagnostic certainty and increasing sensitivity for bvFTD diagnosis [30;37]. The need for cautious use of these new criteria with an increased sensitivity but also less restrictive exclusion features, especially in the psychiatric differential diagnosis, has been stressed by others as well [38]. Nonetheless, it is stated that a bvFTD diagnosis cannot be made in the presence of an explanatory psychiatric condition. The definition of 'dementia' as given in the DSM-IV does not capture the clinical FTD syndrome [15]. The DSM-5 criteria for 'cognitive disorders' have been adapted in order to include neurodegenerative disorders not presenting with memory decline as a first symptom, making them more fitting for bvFTD [16]. Still, the clinician must decide if the cognitive deficits are not primarily attributable to another mental disorder in which case no neurocognitive disorder may be diagnosed. Vice versa, before diagnosing a psychotic or mood disorder according to the DSM, one must exclude the possibility the symptoms may be caused by an organic or neurodegenerative disorder. This illustrates clearly that in clinical practice, in the absence of definitive biomarkers, the diagnostic dilemma "bvFTD or psychiatry" is not solved by simply applying the different sets of clinical consensus criteria.

The sensitivity of neuroimaging for bvFTD is about 50-63.5 % for MRI and about 81-90% for [$^{18}$F]FDG-PET within a memory clinic cohort [39-42]. However, neuroimaging may reveal frontal atrophy or hypofrontality in psychiatric patients as well, compromising the specificity of these investigations [18;43-46]. This is emphasized by the considerable group of subjects in our cohort with initially a *probable* bvFTD diagnosis, based on clinical features and MRI or [$^{18}$F]FDG-PET findings, in which the diagnosis was changed into

a psychiatric disorder. The diagnostic change after follow-up was based upon clinical findings, increasingly suggesting a psychiatric origin of the complaints, as well as upon the absence of progression of neuroimaging abnormalities. So although neuroimaging is very valuable in a bvFTD diagnosis, the evaluation of further disease progression and imaging progression over time remains important. Notably, in all patients with an initial *probable* bvFTD diagnosis that was changed into a psychiatric diagnosis, the MRI findings were rated as normal and not suggestive of FTD, whereas the [$^{18}$F]FDG-PET was rated as abnormal. Therefore, especially the limited specificity of hypofrontality on [$^{18}$F]FDG-PET for bvFTD within a cohort including psychiatric disorders and not just dementia patients, should be prospectively studied in more detail, preferably with considerable follow-up or neuropathological confirmation.

Part of our cohort shows clinical similarities with patients labeled as the 'benign bvFTD-phenocopy syndrome' by others [47]. This phenocopy-syndrome concerns patients, in whom clinical characteristics indistinguishable from *possible* bvFTD are found, but no functional decline nor neuroimaging abnormalities have been found. More evidence starts to emerge that atypical psychiatric disorders might be causing this so-called phenocopy syndrome and that psychiatric consultation might reveal treatable disorders, not always fitting the definition of a major psychiatric disease [14;48]. Interestingly, also part of our cohort with a psychiatric diagnosis did not officially fulfill the criteria for a major psychiatric diagnosis when strictly applied [48]. The subgroup of our cohort in which the diagnosis changed from *possible* bvFTD into a psychiatric disorder might fulfill this phenocopy syndrome definition. Nonetheless, our study shows a significant group of patients that do not fulfill the phenocopy description, since they do show hypometabolism on [$^{18}$F]FDG-PET. A subgroup however, initially considered a *probable* bvFTD group, also had its diagnosis changed into an typical or atypical psychiatric disorder after follow-up, and are therefore not expected to show any more progress over time. This suggests that carefully screening patients psychiatrically is indicated in a larger group of subjects, and not just those fulfilling the 'phenocopy' definition. More prospective research is needed to further characterize this group in which screening is beneficial.

In our cohort none of the baseline characteristics differentiated between the three diagnostic groups. For clinical practice is it important to note that not only the informant based behavioral screening instruments, but also the widely used baseline MMSE and FAB did not differentiate between bvFTD and psychiatric disorders. This is in line with earlier findings: neuropsychological tests may help to identify mild to moderate bvFTD cases, but early bvFTD usually shows intact cognitive functions and the most often displayed executive dysfunction is also frequently seen in psychiatric disorders [20;49]. It must be noted that the examined cohort is part of a larger cohort focusing on early recognition of bvFTD [32]. Therefore all diagnoses were made in early staged disorders and the correct diagnosis may therefore be more difficult to discern from the differential diagnosis compared to more advanced cases.

Since we failed to identify clinically distinguishing features in the cognitive and behavioral screening, we would suggest consulting a psychiatrist in all *possible* and *probable* bvFTD cases in the early diagnostic phase and during follow-up.

Even though no statistically significant differences between the main diagnostic groups were found for sex, an interestingly higher number of subjects in whom diagnosis was changed from bvFTD towards a psychiatric diagnosis were male (9 out of 10). Also in the bvFTD phenocopy syndrome in previous research male gender predominated [47]. Further research should clarify if indeed males are more prone to be misdiagnosed as bvFTD in psychiatric disorders. This would be an interesting topic to study, as in women the opposite seems to hold: women showed to receive a psychiatric misdiagnosis in actual bvFTD more often compared to men [13]. Two cases revealed a pathologic mutation, responsible for the bvFTD syndrome. Their clinical pictures underline the known overlap between PGRN and C9orf72 repeat expansion on the one hand and psychiatric frontal syndromes on the other hand.

To our knowledge, this is the first prospective multidisciplinary study to investigate bvFTD misdiagnosis in primary psychiatric disorders. Our results are of great clinical relevance and strongly suggest incorporating a multidisciplinary approach when it comes to bvFTD early diagnosis and critically reviewing the diagnosis over time. Our data illustrate that the clinical profiles and in some cases the neuroimaging findings of the psychiatric patients in which a bvFTD misdiagnosis was made vividly mimic a bvFTD profile, considering the complaints mentioned by patients and their relatives. It strengthens our study that we blinded both the neurologist and the psychiatrist in the diagnostic process for each other's interpretations and results.

This study has several limitations. Our study was performed in a tertiary center. Therefore, our results cannot easily be extrapolated to a general population. Possibly, the number of misdiagnoses in our cohort is an underestimation of that in a general memory clinic due to the expertise available. On the other hand, it may be that more complex cases are referred to a tertiary center in the first place. Secondly, the study design shows that a consulting psychiatrist during follow-up is essential for identifying both bvFTD misdiagnoses and psychiatric diagnoses. Nonetheless, since the bvFTD differential diagnosis is complex and primary psychiatric disorders have no diagnostic gold standard and often have an atypical phenotype in the older population we strongly advise the multidisciplinary approach used in this study for future clinical practice. Especially in male patients, in patients with multiple psychiatric of psychological disorder traits and in patients merely fulfilling *possible* bvFTD, the FTCD criteria must be applied with caution and alternative diagnoses should be considered again during follow-up.

Furthermore, the used gold standard of two years follow-up may have been too short in some patients. It is hard to come by large numbers of suspected bvFTD subjects for prospective research, but we recommend future repetition of the study in a larger cohort,

ideally with a full genetic screening or neuropathological confirmation to increase diagnostic certainty.

Our study results stress that not only the already known risk of making a psychiatric misdiagnosis in case of bvFTD is a pitfall to recognize [13]. Also, a bvFTD misdiagnosis in case of a psychiatric disorder could be an increasingly common scenario due to improved knowledge of bvFTD. Our findings suggest a limited specificity and a limited positive predictive value of the FTDC criteria. Further research on the factors discriminating bvFTD from psychiatric disorders is needed.

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