Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2016;41:210–219

DOI: 10.1159/000444849
Accepted: February 19, 2016
Published online: May 5, 2016

1420–8008/16/0414–0210$39.50/0
www.karger.com/dem

Original Research Article

Diagnostic Accuracy of the Frontotemporal Dementia Consensus Criteria in the Late-Onset Frontal Lobe Syndrome

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Key Words

Frontotemporal dementia · Neuropsychology/behaviour · Psychiatric disorders · International consensus criteria for behavioural variant FTD

Abstract

Background/Aims: We aimed to prospectively assess the diagnostic accuracy of the revised criteria for behavioural variant frontotemporal dementia (bvFTD) among subjects presenting with a frontal lobe syndrome in middle-late adulthood. ***Methods:*** Patients were included based on a predominant behavioural clinical presentation, a Frontal Behavioural Inventory (FBI) score of ≥11 and/or a Stereotypy Rating Inventory (SRI) score of ≥10. At baseline, the fulfilment of the international consensus criteria for behavioural variant FTD (FTDC) was systematically recorded. The 2-year follow-up consensus diagnosis was used as the gold standard to calculate sensitivity and specificity of the FTDC criteria for possible and probable bvFTD. ***Results:*** Two-year follow-up data were available for 116 patients (85%). Two-year follow-up consensus diagnoses consisted of probable/definite bvFTD (n = 27), other dementia (n = 30), psychiatric disorders (n = 46) and other neurological disorders (n = 13). Sensitivity for possible bvFTD was 85% (95% CI 70–95%) at a specificity of 27% (95% CI 19–37%). Sensitivity for probable bvFTD was 85% (95% CI 69–95%), whereas their specificity was 82% (95% CI 73–89%). ***Conclusions:*** We found a good diagnostic accuracy for FTDC probable bvFTD. However, the specificity for FTDC possible bvFTD was low. Our results reflect the symptomatic overlap between bvFTD, other neurological conditions and psychiatric disorders, and the relevance of adding neuroimaging to the diagnostic process.

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DOI: 10.1159/000444849

Introduction

Behavioural variant frontotemporal dementia (bvFTD) is a clinical syndrome characterized by insidious changes in personality, behaviour and executive functions. It is the second most common early-onset dementia after Alzheimer's disease (AD) [1–4]. In the absence of definitive biomarkers, the diagnosis is based on clinical criteria for bvFTD developed by an international expert consortium (FTDC) [5]. These criteria mainly focus on behavioural/cognitive features that define the bvFTD syndrome (possible bvFTD). For a diagnosis of probable bvFTD, the syndrome has to be accompanied by functional decline over time and the presence of frontotemporal abnormalities on neuroimaging. The revised diagnostic criteria have superior sensitivity over the criteria by Neary et al. [6–8]. Based on autopsy verified bvFTD cases, the sensitivity of the revised criteria for FTDC probable bvFTD is 76% and for possible bvFTD 86% [5].

Although the diagnostic accuracy of the FTDC criteria for bvFTD thus appears to be quite high, in clinical practice the differential diagnosis between bvFTD and psychiatric disorders forms a major dilemma [9–11]. The great symptomatic overlap between bvFTD and psychiatric disorders might affect the diagnostic accuracy of the FTDC criteria in this context. Since psychiatric disorders are treatable, early recognition of a psychiatric origin of frontal symptoms is relevant. Moreover, in clinical trials for bvFTD, these possible bvFTD cases with underlying psychiatric disorders have to be excluded.

In the present study, we therefore set out to prospectively determine the diagnostic accuracy of the revised criteria for possible and probable bvFTD among a clinically relevant cohort of subjects with a late-onset frontal lobe syndrome (LOF).

Methods

Patients

The LOF study is a multi-centre observational and prospective follow-up study of subjects who develop behavioural changes during middle to late adulthood [12]. Behavioural changes in 137 patients consisted of apathy, disinhibition and/or compulsive/stereotypical behaviour, and patients were between 45 and 75 years of age. Patients were recruited from the Amsterdam Dementia Cohort and the GGZ InGeest Department of Old Age Psychiatry, Amsterdam, the Netherlands, between April 2011 and June 2013 [13]. Patients were included in the study when behavioural symptoms dominated the presentation and when the score on the Frontal Behavioural Inventory (FBI) [14] was ≥11 or the Stereotypy Rating Inventory (SRI) [15] score was ≥10. High scores on the FBI or SRI indicate behavioural disturbances or stereotypy. The FBI items included: apathy, aspontaneity, indifference/emotional flatness, inflexibility, disorganization, inattention, personal neglect, logopenia, aphasia and verbal apraxia, comprehension (semantic) deficit, alien hand and/or apraxia, perseveration/obsessions (stereotypy), hoarding, inappropriateness, excessive jocularity, poor judgment and impulsivity, restlessness/roaming, irritability, aggression, hyperorality/food fads, hypersexuality, utilization behaviour, incontinence. The SRI assesses five distinct stereotypical symptoms: disturbances in eating and cooking behaviours, roaming, speaking, movements and daily rhythm. Exclusion criteria of the LOF included: (1) an already established diagnosis of dementia or a psychiatric disorder that could explain behaviour problems; (2) Mini-Mental State Examination (MMSE) no more than 18; (3) medical history, including traumatic brain injury, mental retardation and drugs or alcohol abuse; (4) lack of a reliable informant; (5) insufficient communicative skills of either patient or the closest informant (language, serious hearing impairment or behavioural disturbances, including threatening or physical aggression); (6) acute onset of behavioural problems; (7) clinically apparent aphasia or semantic dementia, and (8) MRI contraindications.

Diagnostic Work-Up

All patients underwent full neurological (Y.A.L.P.) and psychiatric examination (A.D. or C.J.K.) between April 2011 and June 2013. The examinations were contemporaneous with cognitive screening tests and

neuropsychological test battery. Cognitive screening tests included the MMSE and the Frontal Assessment Battery (FAB). Psychiatric evaluation included applying the Montgomery Aberg Depression Rating Scale (MADRS) for depressive symptoms, the positive and negative symptom scale for psychotic symptoms (PANSS), and the MINI-Plus diagnostic interview to assess psychiatric disorders. The neuropsychological test battery included tests that cover attention and concentration, verbal and visual memory, working memory, semantic memory, linguistic and visuospatial skills, and executive functioning including tasks testing abilities of planning, inhibition problem solving, logical reasoning, mental flexibility, emotion recognition and social cognition. All patients underwent an MRI scan of the brain, acquired with a 3-tesla Signa HDxt scanner (GE Medical Systems, Milwaukee, Wis., USA) using a standard dementia protocol [13]. In case of a normal or insufficiently explanatory MRI at baseline, an ^{18}F-FDG-PET scan was performed within 3 months after MRI, using an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, Tenn., USA). CSF was obtained with a lumbar puncture. 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 CSF Tau, CSF pTau181 and CSF Aβ_{1-42} concentrations took place using sandwich ELISAs (Fujirebio/Innogenetics, Belgium) on a routine basis [13]. All patients with a positive family history for early-onset dementia were referred for clinical genetic counselling. If deemed appropriate, genetic screening included the MAPT (n = 9), GRN (n = 7), PSEN1 (n = 2) and APP (n = 0) genes. In all subjects in whom DNA was available (n = 137), C9orf72 hexanucleotide repeat expansion was screened for, given the great symptomatic overlap with psychiatric disorders and long disease courses that have been described in this mutation type [16–20]. The study was approved by the Medical Ethical Committee of the VU Medical Centre, Amsterdam.

FTDC Criteria

At baseline, the FTDC criteria for possible and probable bvFTD were systematically applied in each patient, using information from the psychiatric and neurological examination, informant-based history, results of the neuropsychological test battery and neuroimaging results. The interview was supported by the FBI and SRI questionnaires in all cases. Since a change of daily functioning was the reason for presentation at the memory or psychiatric clinic in all cases, functional decline was considered present in all included subjects. The MRI scans of the brain and FDG-PET scans were visually assessed by an experienced neuroradiologist (F.B. or M.P.W.) and an experienced nuclear medicine specialist (B.N.M.B.) who were both blinded to the patients' complaints and medical history. At baseline, a consensus diagnosis between the neurologist and the psychiatrist was made. After 2-year follow-up, neuropsychiatric questionnaires, neuropsychological test battery and MRI of the brain were repeated, and a final multidisciplinary diagnosis was established. Diagnoses were based on the published consensus guidelines for dementia, and the psychiatric diagnoses were based on current psychiatric criteria [21–25]. Using the follow-up diagnosis as the gold standard, sensitivity and specificity of the diagnostic criteria for FTDC possible and probable bvFTD at baseline were calculated. We also determined the sensitivity and specificity of the six individual clinical features for bvFTD [behavioural/cognitive symptoms (A–F)] [5].

Diagnoses at 2 Years and Attrition

In this study, we included all patients of the LOF cohort (n = 137). The selected cohort consisted of 116 cases, of whom 27 patients were diagnosed with probable/definite bvFTD at 2-year follow-up. Eighty-nine patients received a non-bvFTD diagnosis. A description of how the patients were selected is shown figure 1. We excluded 3 patients from the final analysis with 2-year follow-up diagnosis of possible bvFTD. These patients can be considered as having benign bvFTD phenocopy syndrome; however, due to the open discussion on this issue, we excluded these patients [26, 27]. Another 3 patients who died without post-mortem examination were excluded. Fifteen patients were lost to follow-up, whereby these participants withdrew from the study or could not be contacted.

Data Analysis

Data analysis was performed using IBM SPSS statistics version 20.0 (IBM SPSS Statistics, Armonk, N.Y., USA). The calculation of sensitivity and specificity for the clinical criteria for possible and probable bvFTD and the six individual items were calculated using 2 × 2 tables. Comparisons of age, MMSE, FAB and FBI between groups were made using independent t tests. For the SRI, we used the Mann-Whitney test. Comparisons of sex and education between groups were made using χ^2 tests.

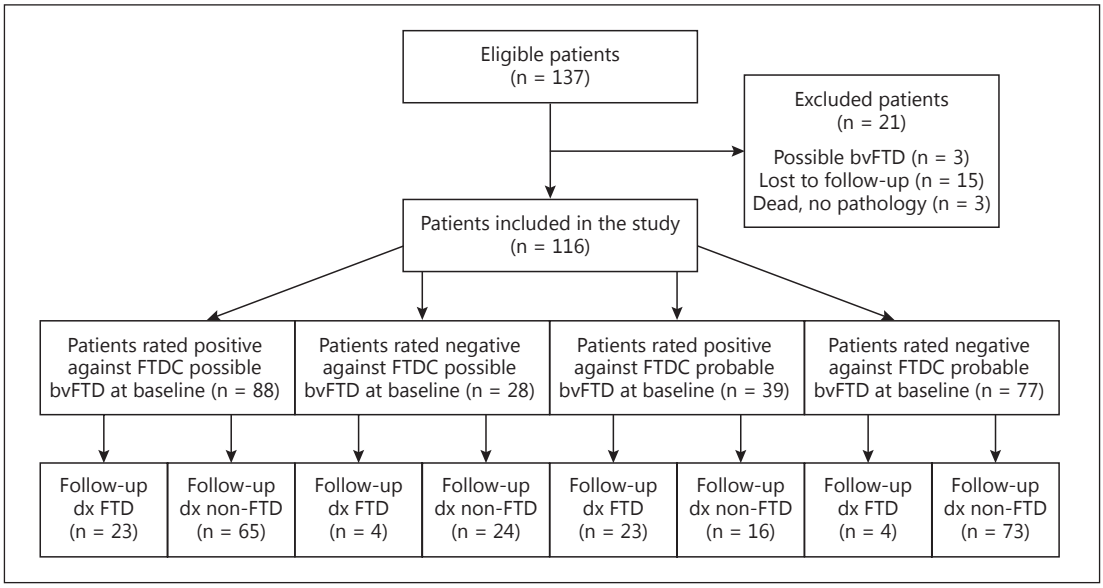

Fig. 1. Flowchart demonstrating patient selection in this study.

Table 1. Clinical and demographic characteristics

Characteristics	FTD (n = 27)	Non-FTD (n = 89)	p value
Men, n (%)	16 (59.2)	71 (80.0)	0.031[b]
Age, years	62.9 (6.7)	61.7 (6.9)	0.415
Education[a]	4.6 (1.4)	4.7 (1.2)	0.217[b]
MMSE	26.1 (2.6)	26.3 (2.8)	0.756
FAB	14.4 (4.0)	14.6 (3.1)	0.975
FBI	26.3 (10.4)	24.2 (9.3)	0.321
SRI	16.0 (10.8)	5.4 (7.4)	0.000[c]

Data are mean (standard deviation) unless otherwise stated. Significance was accepted at $p \leq 0.05$; independent t tests, unless otherwise stated. [a] Verhage Scale score. [b] χ^2 test. [c] Mann-Whitney test.

Results

Clinical and Demographical Characteristics

The clinical and demographical characteristics of patients with bvFTD and patients with other diagnoses (non-bvFTD) are presented in table 1. In the non-bvFTD group, the male sex was significantly more prevalent than in the bvFTD group. The SRI score was significantly higher in bvFTD compared to non-bvFTD patients. There were no significant differences in the other clinical and demographical characteristics.

Table 2 gives an overview of the 2-year follow-up diagnoses. There were 23 (19.3%) patients with probable bvFTD and 4 (3.4%) patients with definite bvFTD. Of these, 3 patients carried a known pathogenic mutation. One patient had a progranulin mutation, presenting only with apathy. Two patients had a C9orf72 hexanucleotide repeat, one of whom presented with all the clinical criteria apart from hyperorality and developed motor neuron disease at clinical and neurophysiological evaluation. The second subject carrying the repeat showed

Dement Geriatr Cogn Disord 2016;41:210–219

DOI: 10.1159/000444849

Table 2. Diagnoses at follow-up (t = 2)

	Frequency	
	n	%
Subjective cognitive decline	5	4.2
AD	7	5.9
Probable bvFTD	23	19.3
FTD-ALS	4	
Definite bvFTD	4	3.4
Histopathological		
Tauopathy	1	
Pathogenic mutation		
C9orf72 expansion	2	
GRN mutation	1	
Possible bvFTD	3	2.5
Dementia with Lewy bodies	4	3.4
Vascular cognitive impairment	7	5.9
Other dementias	12	10.1
Progressive supranuclear palsy	5	
Huntington's disease	1	
Corticobasal degeneration	1	
Semantic dementia	3	
Others	2	
Neurologic disorders	8	6.7
Parkinson's disease dementia	2	
Multiple sclerosis	2	
Limbic encephalitis	1	
Sleep-disorder	1	
Postanoxic encephalopathy	2	
Psychiatric disorders	46	38.6
Schizophrenia	1	
Major depression	12	
Minor depression	4	
Obsessive compulsive disorder	1	
Bipolar disorder	7	
Autism spectrum disorder	3	
Personality disorder	3	
Relationship problems	6	
Other psychiatric disorders	9	
Total	119[a]	100

[a] With the exclusion of possible bvFTD (116 cases), percentages measured on n = 119.

only apathy and loss of empathy at clinical evaluation. One patient with a clinical diagnosis of probable bvFTD had progressive, behavioural disinhibition, apathy/inertia and was autopsied after 1-year follow-up. Widespread tauopathy in the form of tangles, pre-tangles and threads predominantly in the temporal and parietal cortices as well as amygdala were present [28]. In 4 patients, the diagnosis of probable bvFTD was established with a high degree of certainty, without a known pathogenic mutation but with clinical signs of motor neuron disease and neurogenic changes at electromyography. Patients diagnosed with other types of dementia had AD (n = 7), vascular cognitive impairment (n = 7) and dementia with Lewy bodies (n = 4). Parkinson's disease (n = 2), multiple sclerosis (n = 2), histopathologically confirmed limbic encephalitis (n = 1) and postanoxic encephalopathy (n = 1) constituted the group of other neurological disorders. Forty-six patients had a psychiatric disorder

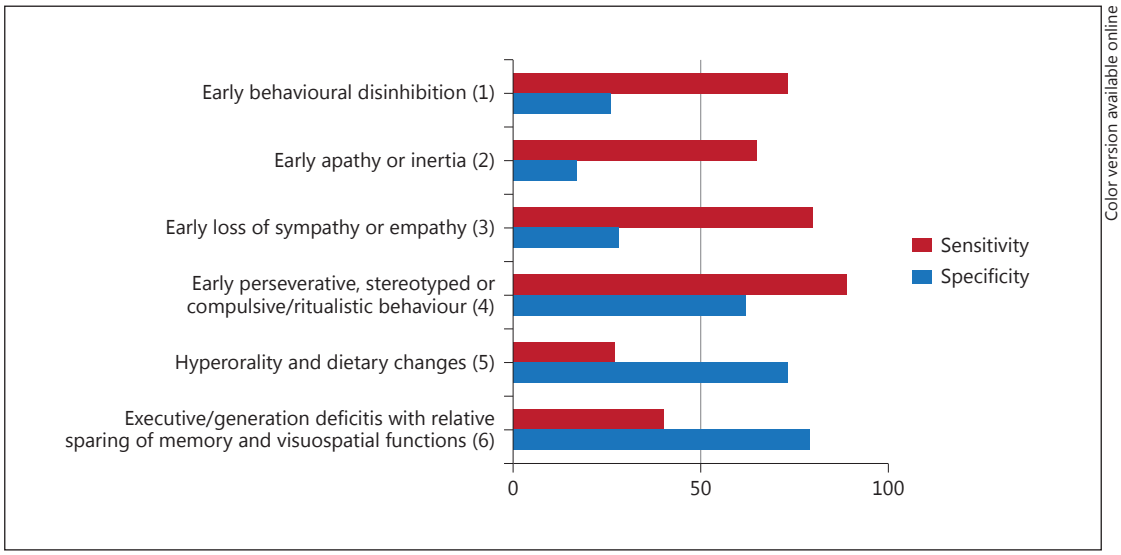

Fig. 2. Sensitivity and specificity of the individual clinical features. (1) Frequency 74%, sensitivity = 0.73 (95% CI 0.54–0.87), specificity = 0.26 (95% CI 0.17–0.35). (2) Frequency 79%, sensitivity = 0.65 (95% CI 0.46–0.82), specificity = 0.17 (95% CI 0.10–0.25). (3) Frequency 74%, sensitivity = 0.81 (95% CI 0.63–0.93), specificity = 0.28 (95% CI 0.19–0.38). (4) Frequency 49%, sensitivity = 0.89 (95% CI 0.73–0.97), specificity = 0.62 (95% CI 0.52–0.72). (5) Frequency 27%, sensitivity = 0.27 (95% CI 0.13–0.46), specificity = 0.73 (95% CI 0.64–0.82). (6) Frequency 25%, sensitivity = 0.40 (95% CI 0.23–0.60), specificity = 0.79 (95% CI 0.70–0.86).

(38.6%). The most common psychiatric diagnoses were major depression (n = 12) and bipolar disorder (n = 7). None of the patients in the non-FTD group carried a known pathogenic mutation.

FTDC Criteria in the Final Cohort

At baseline, 76% of the patients met 3 or more of the core criteria for possible bvFTD (n = 88), and 34% fulfilled the core criteria for probable bvFTD (n = 39), regardless of the follow-up diagnosis. In the patients fulfilling FTDC possible bvFTD, the mean number of the individual cognitive and behaviour features as defined by the core clinical criteria was 3.8 (SD 0.9). Among the patients fulfilling FTDC probable bvFTD, there were 23 cases with frontal and/or temporal atrophy on MRI and 20 cases with frontal and/or temporal hypometabolism frontotemporal on FDG-PET. The patients that fulfilled probable bvFTD without having a follow-up diagnosis of bvFTD consisted of psychiatric disorders (n = 10), other neurodegenerative disorders (n = 4) and other neurological disorders (n = 2).

Sensitivity and Specificity for Probable and Possible bvFTD

The sensitivity of the FTDC criteria for probable bvFTD was 85% (95% CI 69–95%), whereas specificity was 82% (95% CI 73–89%). The sensitivity of the FTDC criteria for possible bvFTD was 85% (95% CI 70–95%) at a specificity of only 27% (95% CI 19–37%). Figure 2 shows the sensitivity and specificity of the individual clinical features. Overall, the specificities for behavioural disinhibition (26%, 95% CI 0.17–0.35), apathy or inertia (17%, 95% CI 0.10–0.25) and loss of sympathy/empathy (28%, 95% CI 0.19–0.38) were the lowest. Perseverative, stereotyped or compulsive behaviour had the highest sensitivity (89%, 95% CI 0.73–0.97) and a high specificity (62%, 95% CI 0.52–0.72).

Dement Geriatr Cogn Disord 2016;41:210–219
DOI: 10.1159/000444849

Discussion

In this clinically relevant cohort of subjects with a LOF, we found a sensitivity of 85% and a specificity of only 27% for the FTDC criteria for possible bvFTD. This indicates that the mere presence of three or more clinical symptoms is not enough for the diagnosis of bvFTD, since many other clinical conditions may present similarly. When adding imaging findings indicating frontotemporal changes, specificity increased to 82%, thereby reflecting the relevance of frontotemporal changes on neuroimaging for a diagnosis of bvFTD in patients with a LOF. The sensitivity of 100% was not reached due to 3 cases that met definite bvFTD (one autopsy and two mutation-confirmed diagnosis), but did not fulfil the criteria for possible bvFTD.

We found higher sensitivities for possible and probable bvFTD than in the autopsy-confirmed FTDC cohort [5]. In another recently published retrospective, blinded, single-rater, case-by-case review of a neuropathological FTLD cohort, the sensitivity for probable bvFTD was 80 and 93% for possible bvFTD [29]. These lower sensitivities, compared to our study, could be related to the threshold scores on the FBI and SRI required for inclusion into our study, whereby certain items, such as disinhibition and apathy, overlap with the clinical criteria for bvFTD. Specificity was not measured in these studies. In a retrospective, autopsy-confirmed early-onset dementia cohort, the sensitivity for probable bvFTD was found to be 85 and 95% for possible bvFTD, which is also substantially higher than the sensitivities of the FTDC study [30]. This may be due to the less atypical presentations of bvFTD patients in this study, including early-onset dementia cases, whereas the most atypical bvFTD cases in the FTDC study were generally older. The specificity for probable bvFTD was 95, and 82% for possible bvFTD. These high specificities compared to our findings are probably the result of the selected dementia cohort in this study which included very few patients with psychiatric and vascular diseases that can mimic bvFTD [30]. Two studies of a cohort of patients carrying the C9orf72 hexanucleotide repeat expansion found significantly lower sensitivities of the FTDC criteria for possible bvFTD (75 and 60%) and probable bvFTD (64 and 38%) [19, 20]. The lower sensitivities in these studies are probably due to the specific phenotype of the C9orf72 hexanucleotide repeat expansion with early behavioural and psychiatric symptoms, indicating the dilemma of differentiating between bvFTD and psychiatric disorder when using the FTDC criteria.

The individual behavioural and cognitive features of the FTDC showed differences in sensitivity and specificity. Whereas the hyperorality/dietary changes and the neuropsychological profile had a high specificity for bvFTD (73 and 79%, respectively), their sensitivity was low. In contrast, the high sensitivity (89%) and lower specificity (62%) for early perseverative, stereotyped or compulsive/ritualistic behaviour indicates the importance to assess this feature in patients with a frontal lobe syndrome. These findings corroborate the significant differences in the SRI score we found between bvFTD and other clinical conditions at baseline. The behaviour feature 'apathy and inertia' has a very low specificity for bvFTD in an LOF, being also common in depression and AD. Our findings differ from the autopsy-confirmed early-onset dementia cohort, where specificities for the individual behavioural features were relatively high, especially for early loss of sympathy or empathy (90%) and early perseverative, stereotyped or compulsive/ritualistic behaviour (85%) [30]. Again, these high specificities are probably the result of the inclusion of the selected dementia cohort. In contrast to our study, we included subjects based on their symptom profile. As a consequence, the specificities are bound to be lower.

A main finding of the present study is the important role of frontotemporal changes on neuroimaging in increasing the probability of bvFTD. Although we found a relatively high specificity of 82% for probable bvFTD, which is mainly influenced by the neuroimaging findings, still a proportion of patients (21.6%) with other diagnoses remain with neuroimaging changes as

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described in the FTDC. This group consists of psychiatric disorders (n = 15), neurodegenerative disorders (n = 7) and other neurological disorders (n = 3), indicating the need for additional biomarkers and clinical follow-up for long-term evaluation of the diagnosis.

In this study, we clearly demonstrate the symptomatic overlap between bvFTD, psychiatric disorders and other neurodegenerative disorders. Seventy-six percent of the final cohort met 3 or more of the core criteria for possible bvFTD, as they had a wide range of clinical diagnoses. These findings are in line with previous studies. Several studies showed that AD is the most common misdiagnosis in early FTD [31–33]. Another study reports that patients with bvFTD received a prior primary psychiatric diagnosis in 52.2% of cases [9]. Most psychiatric misdiagnoses were major depression disorder, bipolar disorder or schizophrenia [9, 10, 33]. As the correct diagnosis is the cornerstone of patient's management, misdiagnosis should be avoided to prevent treatment delay. Furthermore, a correct diagnosis of bvFTD has direct implications for heritability, prognosis and patient management [34, 35].

One of the strengths of the current study is the size of the patient cohort and its study design. Patient inclusion was based on their symptom profile, thereby closely resembling routine clinical practice for the neurologist and psychiatrist. Another important strength is the prospective design of our study since retrospective rating of clinical criteria is hampered by recollection bias and incomplete documentation. On the other hand, the rating of behavioural features is always influenced by the subjective judgment of both informants and healthcare specialists.

A limitation of this study is that a definite FTD diagnosis was based on autopsy and genetic testing in a limited number of cases, and had to rely on the clinical diagnosis at 2-year follow-up as gold standard. For extremely slowly progressive cases of bvFTD, such as those caused by the C9orf72 hexanucleotide repeat expansion, this follow-up duration might be too short. In the vast majority of our cases, however, screening for this mutation was negative. Furthermore, it is important to bear in mind that according to the FTDC exclusion criteria, when the clinical picture is better accounted for by another medical condition such as psychiatric disorders, the bvFTD diagnosis is excluded. We have not taken into account these exclusion criteria in our baseline data, since diagnoses at baseline were not definite.

In summary, we found a good diagnostic accuracy for FTDC probable bvFTD. However, the specificity for FTDC possible bvFTD was low. Our results reflect the overlap with psychiatric or other neurological disorders. These findings suggest that complementary and disease-specific biomarkers might further increase the diagnostic specificity of bvFTD. Moreover, since our results show that psychiatric disorders can mimic bvFTD regarding both clinical and neuroimaging features, we advocate systematic psychiatric evaluation in the work-up of bvFTD.

Acknowledgements

The Alzheimer Centre receives unrestricted funding from various sources through the VUmc Fonds. Dr. Krudop received a fellowship from the KPN Mooiste Contactfonds. Dr. Pijnenburg received a personal fellowship from the Dutch Brain Foundation.

Disclosure Statement

Dr. Prins serves on the advisory board of Boehringer Ingelheim and Forum, and has provided consultancy services for Sanofi. He has been a speaker at symposia organized by Janssen and Novartis and receives research support from Alzheimer Nederland (project No. WE.03-2012-02). Dr. Scheltens has received grant support (for the institution) from GE Healthcare, Danone Research, Piramal and MERCK. In the past 2 years he has received consultancy/speaker fees (paid to the institution) from Lilly, GE Healthcare, Novartis, Forum, Sanofi, Nutricia, Probiodrug and EIP Pharma. The other authors report no disclosures.

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