Identifying Specific Clinical Symptoms of Behavioral Variant Frontotemporal Dementia Versus Differential Psychiatric Disorders in Patients Presenting With a Late-Onset Frontal Lobe Syndrome

Annemiek Dols, MD, PhD[a,*]; Saskia van Liempt, MD, PhD[a]; Flora Gossink, MD[b]; Welmoed A. Krudop, MD[b]; Sietske Sikkes, PhD[b]; Yolande A. L. Pijnenburg, MD, PhD[b]; and Max L. Stek, MD, PhD[a]

ABSTRACT

Objective: Early differentiation between psychiatric disorders and behavioral variant frontotemporal dementia (bvFTD) is of paramount importance in patients with the late-onset frontal lobe syndrome. As bvFTD in patients will deteriorate, psychiatric disorders are treatable. To date, misdiagnosis often occurs due to an overlap of symptoms and lack of specific biomarkers. The aim of our study was to investigate whether specific symptoms could separate bvFTD from psychiatric disorders.

Methods: In a naturalistic, prospective, multicenter study, 137 patients (aged 45–75 years, 72% male) with a late-onset frontal lobe syndrome were included based on their scores on the Frontal Behavioral Inventory (FBI) and the Stereotypy Rating Inventory (SRI) from April 2011 to June 2013. In a multidisciplinary consensus meeting, diagnoses were established based on elaborate neuropsychological testing, magnetic resonance imaging, fludeoxyglucose F 18 positron emission tomography, cerebrospinal fluid biomarkers, and clinical examination by a neurologist and a psychiatrist based on the International bvFTD Criteria Consortium for bvFTD and *DSM-IV-TR* criteria for psychiatric disorders.

Results: Forty-four subjects (32.8%) were diagnosed with a psychiatric disorder, 10 (7.3%) with possible bvFTD, and 45 (32.8%) with probable bvFTD. A logistic regression analysis was performed with "psychiatry or bvFTD" as dependent variable and clinical variables (Montgomery-Asberg Depression Rating Scale [MADRS], SRI, FBI) and demographics as independent variables. A positive history of psychiatric illness, male gender, lower SRI scores and higher MADRS scores were predictive of psychiatric disorders, explaining 65.2% of the variance in diagnosis of psychiatry versus bvFTD ($\chi^2_5 = 60.04$, $P < .001$). On the FBI, symptom level verbal apraxia/aphasia and impulsivity were predictive of bvFTD, whereas irritability was predictive of psychiatric disorders.

Conclusions: In daily clinical practice, specific subtyping of clinical symptoms in patients with late-onset frontal lobe syndrome may aid in differentiating bvFTD patients from psychiatric patients and may provide guidance in patient management.

J Clin Psychiatry 2016;77(10):1391–1395
dx.doi.org/10.4088/JCP.15m09844

[a]Department of Old Age Psychiatry, GGZinGeest, Amsterdam, the Netherlands
[b]Alzheimer Centre and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Centre, Amsterdam, the Netherlands
**Corresponding author:* Annemiek Dols, MD, PhD, Department of Old Age Psychiatry, GGZinGeest, Amstelveenseweg 589, 1081JC, Amsterdam, the Netherlands (a.dols@ggzingeest.nl).

Patients presenting in later adult life with behavioral change consisting of apathy, disinhibition, and/or compulsive or stereotypical behavior, known as late-onset frontal lobe syndrome, have a broad differential diagnosis including neurologic, neurodegenerative, and psychiatric disorders. In fact, any neurologic or neurodegenerative disorder affecting the frontal lobe can cause a combination of different frontal lobe syndrome features, as shown, for example, in Alzheimer's disease[1] and vascular dementia.[2] However, the behavioral variant of frontotemporal dementia (FTD) is characterized by late-onset frontal lobe syndrome,[3,4] with core symptoms of behavioral disinhibition, apathy, stereotyped or compulsive behavior, loss of empathy, hyperorality, and executive deficits.[3] According to the recent international consensus criteria[3] for a behavioral variant FTD (bvFTD) diagnosis, 3 of these 6 core symptoms are mandatory, 5 of which are behavioral. However, if "behavioral disturbance is better accounted for by a psychiatric diagnosis," a diagnosis of bvFTD has to be excluded.[3]

The clinical dilemma is that in the early stages of disease, a diagnosis of probable bvFTD cannot be established, as imaging may not (yet) show a pattern consistent with bvFTD[3] and significant functional decline may not be present or detectable in early stages. Whereas neuroimaging and cerebrospinal fluid biomarkers are of value in the differential diagnosis with vascular dementia and Alzheimer's disease,[5,6] the differential diagnosis with psychiatric disorders relies on clinical judgment.

A retrospective study[7] of 69 bvFTD patients revealed that 50.7% had a psychiatric diagnosis precede the bvFTD diagnosis, a finding indicating that misdiagnosis is common in the early stage of disease. Measures of depression, cognition, functional status, and neuropsychiatric symptoms were unrelated to psychiatric diagnosis in this study.[7]

The aim of our study was therefore to investigate whether, despite the clinical overlap between bvFTD and psychiatric disorders, unique individual symptoms might separate the 2 illness groups. We employed commonly used clinical scales rating frontal, stereotypical, and depressive symptoms to classify our patients. We explored whether depressive symptoms would identify a psychiatric origin of late-onset frontal lobe syndrome, whereas frontal behavior symptoms and stereotypy would be more specific in bvFTD patients.

Clinical Points

- Misdiagnosis in patients with the late-onset frontal lobe syndrome often occurs due to an overlap of symptoms and lack of specific biomarkers. Emphasis on specific clinical symptoms and the use of validated clinical rating scales will improve early detection of a psychiatric origin of late-onset frontal lobe syndrome.
- A positive history of psychiatric illness, male gender, depressive symptoms, and absence of stereotypy were associated with a psychiatric disorder underlying late-onset frontal lobe syndrome. Patients with behavioral variant frontotemporal dementia were characterized by aphasia, verbal apraxia, and impulsivity, but not by irritability.

METHODS

Study Sample

Patients with late-onset frontal lobe syndrome were recruited through the memory clinic of the Alzheimer Center of the VU University Medical Center, Amsterdam, and the psychiatric clinic for the elderly of the mental health institution GGZinGeest Amsterdam, the Netherlands (inpatient and outpatient), from April 2011 to June 2013. Patients were directed to these specialized health care institutions by primary care physicians or a medical specialist for diagnostic procedures. The goal of the study was to explore the causes of late-onset frontal lobe syndrome in both a memory clinic and a psychiatry-based cohort. Patients were included only if they met inclusion criteria and did not meet exclusion criteria as described elsewhere.[8] In summary, late-onset frontal lobe syndrome was defined as behavioral change consisting of apathy, disinhibition, 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) Frontal Behavioral Inventory (FBI)[9] score of 11 or higher or a Stereotypy Rating Inventory (SRI)[10] score of 10 or higher in patients with Mini-Mental State Examination (MMSE)[11] scores of 18 or higher. The low cutoff for FBI and SRI enabled inclusion of patients with an early stage of disease. Patients were excluded if an already established diagnosis could explain the behavioral problems (eg, dementia, psychiatric disorder according to *DSM-IV-TR*[12]), an acute onset of behavioral problems had occurred, or a medical history of traumatic brain injury, mental retardation, or drugs or alcohol dependence was present. Other exclusion criteria were lack of a reliable informant, insufficient communicative skills of either patient or the informant (language, serious hearing impairment, or severe behavioral disturbances including threatening or physical aggression), or magnetic resonance imaging (MRI) contraindications. The study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam. Informed consent was signed by the patient or, if the patient was not sufficiently competent to give a fully informed consent, obtained from the caregiver or legal representative.[13]

A total of 234 patients were screened for eligibility. Thirty-nine (17%) of these patients were excluded on the basis of alcohol or drug dependence (present or past), and 58 (25%) were excluded because of either refusal or incapability to provide informed consent, leaving 137 entering the study.

Diagnostic Procedures

All patients underwent a standardized assessment, including medical history and family history; informant-based history; physical, neurologic, and psychiatric examinations; neuropsychological assessment; laboratory tests; and MRI of the brain acquired on a 3T Signa HDxt scanner (GE Medical Systems; Milwaukee, Wisconsin) following a standard MRI protocol for dementia. In case of normal or insufficiently explanatory MRI results (not explaining frontal dysfunction), a fludeoxyglucose F 18 positron emission tomography scan was performed using an ECAT EXACT HRþ scanner (Siemens/CTI, Knoxville, Tennessee) in 64 patients (32 [64%] with bvFTD and 32 [78%] with psychiatric diagnosis). Neurologic and psychiatric evaluation was performed by both a neurologist and a geriatric psychiatrist. In a multidisciplinary consensus meeting, the neurologist and psychiatrist determined the clinical diagnosis after reviewing the neuropsychological, imaging and cerebrospinal fluid results. Diagnoses were based on the International bvFTD Criteria Consortium[3] for bvFTD, the National Institute on Aging-Alzheimer's Association guidelines[6] for Alzheimer's disease, the National Institute of Neurologic Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria[5] for vascular dementia, the International Consensus Diagnostic Criteria[14] for dementia with Lewy bodies, and the *DSM-IV-TR*[12] for psychiatric disorders.

Clinical Assessment

Demographic data (age, gender, education) were derived from the patients' medical records and confirmed in face-to-face interviews. The assessment of frontal behavioral symptomatology consisted of the MMSE,[11] the Frontal Assessment Battery,[15] the FBI,[9] and the SRI.[10]

The FBI has 24 items; each item can be rated 0 to 3. The FBI items are apathy, aspontaneity, indifference/emotional flatness, inflexibility, disorganization, inattention, personal neglect, loss of insight, 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 behavior, and incontinence. The Dutch version of the FBI has separated "poor judgment" and "impulsivity" into 2 items, and has left out the item "hoarding."

The SRI assesses 5 distinct stereotypical symptoms: disturbances in eating and cooking behaviors, roaming, speaking, movements, and daily rhythm (scoring behavior and severity with a maximum of 12 per item resulting in a

Table 1. Demographic and Clinical Characteristics

Characteristic	Psychiatric Disorder (n = 41)	Behavioral Variant Frontotemporal Dementia (n = 50)	*P* Value
Age, mean (SD), y	60.73 (6.7)	62.33 (6.3)	.24
Male gender, n (%)	34 (83)	31 (62)	.04
Education, median (IQR), y	10 (4)	10 (5)	.49
Disease duration, median (IQR), y	3 (3)	3 (4)	.85
Positive psychiatric history, n (%)	27 (65)	11 (22)	< .01
FBI score, mean (SD)	23.34 (7.9)	25.98 (9.4)	.16
SRI score, median (IQR)	2 (5)	9 (15.5)	< .01
MADRS score, median (IQR)	15 (15)	6 (9)	< .01
MMSE score, mean (SD)	26.61 (2.9)	26.08 (2.6)	.36
FAB score, mean (SD)	15.53 (3.0)	14.33 (3.9)	.12
Use of sedatives, n (%)	3 (7.3)	1 (2.0)	.32
Use of antidepressants, n (%)	21 (51.2)	14 (28.0)	.03
Use of antipsychotics, n (%)	6 (14.6)	3 (6.0)	.29
Hyperreflexia, n (%)	0	1 (2.0)	1.00
Parkinsonism, n (%)	5 (12.2)	6 (12.0)	1.00

Abbreviations: FAB = Frontal Assessment Battery, FBI = Frontal Behavioral Inventory, IQR = interquartile range, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Examination, SRI = Stereotypy Rating Inventory.

maximum score of 60, with higher scores indicating more stereotypical symptoms).

Depressive symptoms were rated with the Montgomery-Asberg Depression Rating Scale (MADRS)[16]; this scale is commonly used to evaluate depressive symptoms during treatment. The MADRS consists of 10 items (sadness [apparent and reported], inner tension, sleep, appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts), each of which can be rated from 0 to 6, with higher scores indicating more depressive symptoms. The Mini-International Neuropsychiatric Interview-Plus[17] was employed to rate Axis I psychiatric diagnostic criteria.

Statistics

Data were analyzed using the Statistical Package of the Social Sciences (SPSS, version 21; IBM Corp, Armonk, New York). For demographic data, group differences between patients with bvFTD and patients with a psychiatric disorder on continuous variables were determined by independent *t* tests. If a variable was not normally distributed after log transformation, a Mann-Whitney test was used. Group differences in categorical variables (gender, psychiatric history) were calculated using χ^2 tests.

Logistic regression analyses were used to investigate the relationship between clinical variables and diagnosis. The linearity of the associations was studied prior to the logistic regression, and variables were categorized if necessary. Due to the exploratory nature of this study, we selected a limited number of variables that would possibly be associated with a psychiatric diagnosis versus bvFTD. For the variables age, gender, education, disease duration, psychiatric history, total FBI score, total SRI score, total MADRS score, total MMSE score and total Frontal Assessment Battery score, we performed univariable logistic regression analyses with a diagnosis of bvFTD as dependent variable. We selected variables showing *P* values < .1 as input for the analyses. In the next step, we combined these independent variables into a single multivariable model to investigate the explained variance. Potential multicollinearity was investigated for the multivariable model using the variance inflation factor for each of the independent variables in the multivariable model using linear regression analyses, and variables were removed if the variance inflation factor was > 5. Subsequently, we performed an additional logistic regression analysis with the subitems of the FBI to determine which frontal behavior was predictive of bvFTD versus psychiatric disorder. Again, we first performed univariable analyses to select a maximum of 9 variables (with a significance level of $P < .1$), which we then entered in a multivariable analysis to investigate the explained variance.

A *P* value of < .05 was considered statistically significant, except when indicated otherwise.

RESULTS

Clinical and Demographic Data

Forty-two subjects (30.7%) were diagnosed with a psychiatric disorder according to *DSM-IV-TR* criteria, mainly consisting of a unipolar mood disorder (n = 25), followed by bipolar disorder (n = 6), autism spectrum disorder (n = 3), schizophrenia (n = 2), and obsessive-compulsive disorder (n = 2). An additional 2 patients had a psychiatric diagnosis as comorbidity (autism and minor depression) without a diagnosis fully explaining their symptoms; therefore, in a total of 44 patients, the working hypothesis was a psychiatric origin of the behavioral disturbance. Fifty-five patients were diagnosed with bvFTD: 10 with possible bvFTD and 45 with probable bvFTD. The remaining patients were diagnosed with dementia (n = 23, 16.8%), a neurologic disease (n = 8), or marital or relationship problems (n = 3) or they did not have an explanatory diagnosis (n = 4).

In 8 subjects, MADRS data were missing; data were available on 41 patients with a psychiatric origin of the complaints (hereafter "psychiatric disorder") and 50 patients with bvFTD. Table 1 demonstrates the clinical characteristics of the study sample. Patients with a psychiatric disorder were more often male ($\chi^2_1 = 4.83$, $P = .04$), had more often a psychiatric history ($\chi^2_1 = 16.97$, $P < .01$), and had a lower SRI total score ($F_{1,89} = 16.39$, $P < .01$) and a higher total MADRS score ($F_{1,89} = 31.07$, $P < .01$).

Patients with a psychiatric disorder used antidepressants significantly more often, but not sedatives or antipsychotics. Findings at neurologic examination, such as hyperreflexia and parkinsonism, were no different between patients with bvFTD or a psychiatric disorder (Table 1).

Specific Clinical Variables of Psychiatric Disorder Versus bvFTD

A psychiatric disorder was associated with a psychiatric history (OR = 8.01; 95% CI, 2.05–31.2), female gender (OR = 0.14; 95% CI, 0.03–0.64), few stereotypic symptoms (low total SRI score, OR = 2.5; 95% CI, 1.38–4.56) and high scores on depression scale (MADRS, OR = 0.17; 95% CI,

Table 2. Clinical Indicators for Psychiatric Disorder Versus Behavioral Variant Frontotemporal Dementia Diagnosis

Indicator	OR (95% CI)	*P* Value
Psychiatric history	8.01 (2.05–31.2)	.003
Female gender	0.14 (0.03–0.64)	.011
FBI total score	1.05 (0.97–1.13)	.28
SRI (log transformed)	2.50 (1.38–4.56)	.003
MADRS (log transformed)	0.17 (0.06–0.46)	.000

Abbreviations: FBI = Frontal Behavioral Inventory, MADRS = Montgomery-Asberg Depression Rating Scale, OR = odds ratio, SRI = Stereotypy Rating Inventory.

0.06–0.46) (Table 2). The total FBI score was not indicative of bvFTD (OR = 1.05; 95% CI, 0.97–1.13).

The combined predictors psychiatric history, gender, total FBI, SRI, and MADRS explained 65.2% of the variance in diagnosis of psychiatric disorder versus bvFTD ($\chi^2_5 = 60.04$, $P < .001$).

Specific Clinical Symptoms of Psychiatric Disorder Versus bvFTD

The symptoms of the FBI that were significantly indicative for bvFTD were aphasia and verbal apraxia (OR = 3.00; 95% CI, 1.30–6.95) and impulsivity (OR = 2.13; 95% CI, 1.00–4.50). The symptom of the FBI that was significantly indicative for a psychiatric origin was irritability (OR = 0.30; 95% CI, 0.13–0.69) (Table 3).

The combined predictors psychiatric history, gender, and 7 items of total FBI (comprehension [semantic] deficit; aphasia and verbal apraxia; perseveration, obsessions, stereotypy; irritability; poor judgement; impulsivity; restlessness/roaming) explained 45.8% of the variance in diagnosis of psychiatric disorder versus bvFTD ($\chi^2_9 = 55.18$, $P < .001$).

Specific Clinical Variables and Symptoms of Psychiatric Disorder Versus Probable bvFTD

In a post hoc analysis on patients with probable bvFTD versus psychiatric disorder, the combined predictors psychiatric history, gender, total FBI, SRI, and MADRS explained 66.7% of the variance in diagnosis ($\chi^2_5 = 57.54$, $P < .0001$). The combined predictors psychiatric history, gender, and the 7 total FBI items previously mentioned explained 70.9% of the variance in diagnosis of psychiatric disorder versus probable bvFTD ($\chi^2_9 = 62.94$, $P < .0001$).

DISCUSSION

Our data show that a positive history of psychiatric illness, male gender, depressive symptoms, and absence of stereotypy were associated with a psychiatric disorder underlying late-onset frontal lobe syndrome. Patients with bvFTD were characterized by aphasia, verbal apraxia, and impulsivity, but not by irritability.

To ensure that our findings were not biased by possible bvFTD patients who may not convert to probable bvFTD patients in the future, we performed a post hoc analysis on patients with probable bvFTD versus psychiatric disorder.

Table 3. Frontal Behavioral Inventory Items as Indicators for Psychiatric Disorder Versus Behavioral Variant Frontotemporal Dementia Diagnosis

Variable	OR (95% CI)	*P* Value
Psychiatric history	15.4 (3.72–63.5)	.00
Female gender	0.64 (0.13–3.10)	.57
Comprehension (sematic) deficit	1.78 (0.81–3.91)	.15
Aphasia and verbal apraxia	3.00 (1.30–6.95)	.01
Perseveration, obsessions (stereotypy)	1.53 (0.75–3.12)	.24
Irritability	0.30 (0.13–0.69)	.005
Poor judgment	1.28 (0.65–2.54)	.47
Impulsivity	2.13 (1.00–4.50)	.049
Restlessness/roaming	1.04 (0.51–2.14)	.91

Abbreviation: OR = odds ratio.

These analyses exhibited similar findings that were more significant.

To date, 2 studies[18,19] have focused on differentiating bvFTD patients from psychiatric patients. A study[18] in 288 patients (40 FTD, 35 psychiatric disorder, 17 normal controls, 196 neurodegeneration) who were subjected to cognitive testing and completed a checklist for inappropriate behavior followed by multidisciplinary evaluation (neurologist and psychiatrist) was performed to quantify spontaneous social behavior specific to FTD. Compared to healthy controls, FTD patients exhibited unusual calmness, and compared to psychiatric patients, FTD patients were more often found apathetic or disinhibited and unconcerned about meeting clinician expectations. A retrospective analysis[19] of 134 patients with possible FTD with a follow-up duration of 2 years yielded the finding that 27% eventually received a psychiatric diagnosis. There were no differences between FTD patients and non-FTD patients on demographic variables, but the pattern of cognitive progression after 2 years (worse naming and executive dysfunction and preserved constructional ability) was specific to FTD.

A bvFTD clinical phenotype characterized by lack of significant functional decline and normal neuroimaging findings even after extensive follow-up has been termed the "benign phenocopy syndrome," "FTD mimics," or "nonprogressors."[20–22] Psychiatric conditions may contribute to this syndrome due to symptomatic overlap. Recently, our group published a study[23] on 33 "benign phenocopy" cases that had been fully psychiatric evaluated and found that psychiatric and psychological conditions were more prevalent in patients with benign bvFTD phenocopy syndrome than in patients with probable bvFTD. The need for long-term follow-up and genetic testing of phenocopy cases has been illustrated by the relatively stable clinical course that may occur in chromosome 9 open reading frame 72 (C9ORF72) repeat expansion carriers.[24] Predictors for nonprogression in clinical bvFTD appeared to be male gender, better general cognition, poorer everyday skills, poorer self-care, and sleep disturbance at presentation.[25] Distractibility and stereotypic speech were more specific for progressors.

A review[26] on the prodromal phase of bvFTD summarized social misconduct, disinhibition, and indifference to be relatively specific, whereas apathy, irritability, and rigidity were not.

The lack of prospective studies using standardized clinical rating instruments prevents drawing general conclusions on research so far. The application of commonly used clinical rating scales is an important advantage of our study. The naturalistic design of our study and the inclusion based on symptom profile instead of diagnosis are other important strengths, as our sample resembles clinical practice very strongly. Moreover, patients were included from a memory clinic and an old age psychiatry department, restricting referral bias. However, limitations have to be acknowledged; the cross-sectional design does not allow for follow-up of patients with possible significant functional decline, although median disease duration was 3 years at study entry. Furthermore, we used an exploratory regression technique due to limited literature in the field, which might have led to an overestimation of the true associations, and our findings therefore need replication in an independent sample.

Acknowledging the limitations, we note that this study is the first to systematically and prospectively subtype patients with late-onset frontal lobe syndrome. Our data show that total depression and stereotypy scores differentiate between bvFTD and psychiatric disorders and that specific frontal symptoms are unique to bvFTD. This may help in the differential diagnosis of patients with late-onset frontal lobe syndrome, especially when biomarker results remain inconclusive at the early stage of disease. In the near future, advanced techniques such as tau-imaging might shed new light on the differentiation between late-onset frontal lobe syndrome caused by neurodegenerative versus nonneurodegenerative disorders. Meanwhile, more emphasis on specific clinical symptoms and the use of validated clinical rating scales will improve early detection of a psychiatric origin of late-onset frontal lobe syndrome. Although symptomatic treatments can be offered in late-onset frontal lobe syndrome regardless origin, neurodegenerative diseases are progressive and eventually mortal; however, most psychiatric disorders can be treated effectively. In daily clinical practice, much could be gained by a systematic focus on clinical symptoms in patients with late-onset frontal lobe syndrome, as it may differentiate bvFTD patients from psychiatric patients and provide guidance for patient management.

Submitted: January 31, 2015; accepted August 5, 2015.

Online first: July 5, 2016.

Potential conflicts of interest: None of the authors report a conflict of interest.

Funding/support: Dr Pijnenburg received a personal fellowship to perform the late-onset frontal lobe syndrome study from the Dutch Brain Association, The Hague, the Netherlands.

Role of the sponsor: The Dutch Brain Association had no role in the design or in the conduct or publication of the study.

Previous presentation: Dr Dols presented data from this study orally at the 9th International Conference on Frontotemporal Dementia; October 23, 2014; Vancouver, Canada.

REFERENCES

1. Woodward M, Jacova C, Black SE, et al; ACCORD investigator group. Differentiating the frontal variant of Alzheimer's disease. *Int J Geriatr Psychiatry*. 2010;25(7):732–738.
2. Staekenborg SS, Su T, van Straaten EC, et al. Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease. *J Neurol Neurosurg Psychiatry*. 2010;81(5):547–551.
3. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(pt 9):2456–2477.
4. Mackenzie IR, Neumann M, Bigio EH, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. *Acta Neuropathol*. 2010;119(1):1–4.
5. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43(2):250–260.
6. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263–269.
7. Woolley JD, Khan BK, Murthy NK, et al. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry*. 2011;72(2):126–133.
8. Krudop WA, Kerssens CJ, Dols A, et al. Building a new paradigm for the early recognition of behavioral variant frontotemporal dementia: Late Onset Frontal Lobe Syndrome study. *Am J Geriatr Psychiatry*. 2014;22(7):735–740.
9. Kertesz A, Davidson W, Fox H. Frontal Behavioral Inventory: diagnostic criteria for frontal lobe dementia. *Can J Neurol Sci*. 1997;24(1):29–36.
10. Shigenobu K, Ikeda M, Fukuhara R, et al. The Stereotypy Rating Inventory for frontotemporal lobar degeneration. *Psychiatry Res*. 2002;110(2):175–187.
11. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state:" a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
12. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
13. Kim SY, Appelbaum PS, Jeste DV, et al. Proxy and surrogate consent in geriatric neuropsychiatric research: update and recommendations. *Am J Psychiatry*. 2004;161(5):797–806.
14. McKeith IG, Dickson DW, Lowe J, et al; Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65(12):1863–1872.
15. Dubois B, Slachevsky A, Litvan I, et al. The FAB: a Frontal Assessment Battery at bedside. *Neurology*. 2000;55(11):1621–1626.
16. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
17. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33.
18. Rankin KP, Santos-Modesitt W, Kramer JH, et al. Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. *J Clin Psychiatry*. 2008;69(1):60–73.
19. Mendez MF, Shapira JS, McMurtray A, et al. Accuracy of the clinical evaluation for frontotemporal dementia. *Arch Neurol*. 2007;64(6):830–835.
20. Kipps CM, Nestor PJ, Fryer TD, et al. Behavioural variant frontotemporal dementia: not all it seems? *Neurocase*. 2007;13(4):237–247.
21. Kipps CM, Hodges JR, Hornberger M. Nonprogressive behavioural frontotemporal dementia: recent developments and clinical implications of the 'bvFTD phenocopy syndrome.' *Curr Opin Neurol*. 2010;23(6):628–632.
22. Davies RR, Kipps CM, Mitchell J, et al. Progression in frontotemporal dementia: identifying a benign behavioral variant by magnetic resonance imaging. *Arch Neurol*. 2006;63(11):1627–1631.
23. Gossink FT, Dols A, Kerssens CJ, et al. Psychiatric diagnoses underlying the phenocopy syndrome of behavioural variant frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 2016;87(1):64–68.
24. Khan BK, Yokoyama JS, Takada LT, et al. Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. *J Neurol Neurosurg Psychiatry*. 2012;83(4):358–364.
25. Hornberger M, Shelley BP, Kipps CM, et al. Can progressive and non-progressive behavioural variant frontotemporal dementia be distinguished at presentation? *J Neurol Neurosurg Psychiatry*. 2009;80(6):591–593.
26. Hallam BJ, Silverberg ND, Lamarre AK, et al. Clinical presentation of prodromal frontotemporal dementia. *Am J Alzheimers Dis Other Demen*. 2007;22(6):456–467.