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Frontotemporal Dementia Differential Diagnosis in Clinical Practice

A Single-Center Retrospective Review of Frontal Behavioral Referrals

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Abstract

Background and Objectives

Many neurodegenerative syndromes present with impairment of frontal networks, especially frontoinsular networks affecting social and emotional cognition. People presenting with frontal network impairments may be considered for a frontotemporal dementia (FTD) diagnosis. We sought to examine the diagnostic mix of patients referred with frontal network impairments to a single cognitive neurology service.

Methods

A retrospective review was conducted of all patients seen between January 2010 and December 2019 at the Eastern Cognitive Disorders Clinic, a quaternary cognitive neurology clinic in Melbourne, Australia. Patients were included if they met the following criteria: (1) were referred for suspected FTD or with a preexisting diagnosis of a FTD syndrome, (2) were referred for 'frontal behaviors' (i.e., disinhibition, disorganization, poor judgment, loss of empathy, apathy) and/or had an informant report of behavior change, and (3) had available referral documents and clinical consensus diagnosis. Referral diagnosis was compared against final diagnosis adjudicated by a consensus multidisciplinary team. Case details including age of symptom onset, Cambridge Behavioural Inventory-Revised scores, psychiatric history, and Charlson Comorbidity Index were compared against the final diagnosis.

Results

In total, 161 patients aged 42–82 years (mean = 64.5, SD = 9.0; 74.5% men) met inclusion criteria. The commonest final diagnosis was a FTD syndrome (44.6%: 26.7% behavioral variant FTD (bvFTD), 9.3% progressive supranuclear palsy, 6.2% semantic dementia, 1.2% corticobasal syndrome, and 1.2% FTD/motor neuron disease). A primary psychiatric disorder (PPD) was the next commonest diagnosis (15.5%), followed by vascular cognitive impairment (VCI, 10.6%), Alzheimer disease (AD, 9.9%), and other neurologic diagnoses (6.2%). A final diagnosis of bvFTD was associated with higher rates of medical comorbidities and more eating behavior abnormalities compared with a diagnosis of PPD. Screening cognitive tests and preexisting psychiatric history did not distinguish these 2 groups.

Discussion

A broad spectrum of neurologic and psychiatric disorders may present with impairments to frontal networks. Almost half of patients referred had a final FTD syndrome diagnosis, with bvFTD the commonest final diagnosis. People with PPD, VCI, and AD present with similar clinical profiles but are distinguishable using MRI and FDG-PET imaging. Medical and psychiatric comorbidities are common in people with bvFTD.

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Introduction

Our frontal lobes determine our movement, judgment, speech and language, insight, emotions, and social behavior. It is not surprising that frontal networks are affected or impaired in many brain diseases. Patients can present to diagnostic services with multiple impairments of frontal networks (frontal network impairment, FNI), including observed changes in behavior, personality, judgment, and emotions. Sometimes, these are measurable by using tests of executive function,[1] theory of mind,[2] and social and emotional cognition.[3] Each of these impairments is dissociable,[1] i.e., no measurable deficits in executive function in the presence of profound deficits in social and emotional cognition. Frontotemporal dementia (FTD) is the second commonest syndromic diagnosis in people with young-onset dementia.[4] People with FTD usually present with FNI, but people presenting with FNI may have other diagnoses, including a primary psychiatric disorder (PPD), frontal variant of Alzheimer disease (AD),[5] and the phenocopy syndrome of bvFTD.[6,7]

Behavioral variant FTD (bvFTD) is the commonest clinical phenotype of the pathologic spectrum of frontotemporal lobar degeneration (FTLD). bvFTD is characterized by an insidious onset of progressive changes in an individual's behavior and personality, accompanied by deterioration in social cognition and executive function.[8] Other FTD syndromes such as semantic dementia can be associated with often florid behavioral changes.[9] Early and accurate diagnosis of bvFTD remains challenging and has been highlighted as a priority by people with lived experience of dementia[10] and their caregivers.[11] The young age of symptom onset and overlap in the clinical presentation with PPD[12] contribute to misdiagnosis and delays to diagnosis (on average 5–6 years from symptom onset).[13-17] Structural and functional brain imaging changes can be mild and very slowly progressive in early stages of bvFTD and in people with *C9orf72* repeat expansions.[18] This has prompted the development of recommendations to distinguish bvFTD from PPD, based on tests of social cognition, brain imaging, and fluid biomarkers.[13]

Although there is a large literature on diagnostic criteria for FTD syndromes and, more recently, recommendations on criteria to discriminate a PPD from FTD, there are few reports of real-world experience of referrals to cognitive services and diagnostic mix. We asked who is referred for consideration of a FTD diagnosis to cognitive neurology services, and what diagnoses do they have after investigation? We aimed to identify patients referred with FNI to a university hospital cognitive neurology specialist service. We sought to identify clinical factors and discriminators associated with a final bvFTD diagnosis in a cohort of patients seen over a 10-year referral period.

Methods

Clinic Setting

This retrospective case study included patients referred to the Eastern Cognitive Disorders Clinic (ECDC, Melbourne, Australia) between January 2010 and December 2019 with symptoms consistent with FNI. ECDC is a quaternary specialist diagnostic and assessment service based in the eastern suburbs of Melbourne (population ~5.3 million) for individuals referred with atypical and young-onset dementias. Our health care network catchment (Eastern Health) has a catchment of over 950,000 people living in an area spread across 2816 km^2, with 26% from non–English-speaking backgrounds. ECDC also operates as a national referral service as one of the few cognitive neurology clinics in Australia for people whose diagnoses are unclear. Once referred, patients can have indefinite review. This service operates in tandem with the Eastern Health geriatrician-led memory clinic, where patients older than 75 years and those with more typical amnestic concern and greater frailty are usually seen. ECDC operates as a low-volume service with a referral bias for younger people with behavioral or language disturbances as their initial concern. Over the years captured, specialist medical staffing was by 1 cognitive neurologist in 2010–2011, 2 in 2012–2018, and 3 in 2018–2019, with a fellow program from 2015.

Participant Selection

Patients with FNI were identified using the following criteria: clinical referral for (1) a question of 'is this bvFTD?'; (2) 'frontal behavior' (i.e., disinhibition, disorganization, and poor judgment); (3) behavioral change for investigation; or (4) a preexisting bvFTD diagnosis. Participants were included if they had an extant referral, clinical correspondence and investigation reports, and a final consensus diagnosis with appropriate review.

Data Collection

Data were reported as a retrospective case review, guided by principles of reporting from the Standards for Reporting Diagnostic Accuracy (STARD) studies guidelines and other authors.[19]

Demographic and clinical data were entered into a secure REDCap database. All patients completed a detailed demographic questionnaire (i.e., Melbourne Life Questionnaire, modified from the Sydney Life Questionnaire, copyright John Hodges 2010). Informants completed the Cambridge Behavioural Inventory-Revised (CBI-R) questionnaire.[20] Cognitive screening tests including the Mini-Mental State Examination (MMSE)[21] and, from 2011, the Addenbrooke's Cognitive Examination-Revised Edition (ACE-R)[22] were also conducted where possible. Variables extracted included demographic information, medical and psychiatric history, and a detailed family history that asked about neurologic and psychiatric illnesses in first-degree relatives. A retrospective review of the medical record was also performed to extract information including initial referral source, mean age of presentation, presenting symptoms, duration of symptoms, dates of consultations, investigations subsequent to referrals to other clinicians, and provisional diagnoses. The extracted data were also

used to generate the Charlson Comorbidity Index (CCI)[23] as a summary score of medical comorbidities.

Final Consensus Diagnosis

Final consensus diagnosis was determined by a multidisciplinary panel including cognitive neurologists, neuropsychologists, speech pathologists, an occupational therapist, and a cognitive nurse consultant. Case discussion included a presentation of the history and informant report; viewing and rating of MRI and FDG-PET images; neuropsychological, occupational therapy, and speech therapy assessments; and evidence of progression on longitudinal review. We do not have a neuropsychiatrist or aged psychiatrist as part of our multidisciplinary team but are fortunate to have access to expert neuropsychiatry services in Melbourne for cross-referrals and consultation (e.g., Melbourne Neuropsychiatry Unit at the Royal Melbourne Hospital).

Genetic testing was also arranged for those at high risk of genetic syndromes. We note that genetic testing was not available through universal health care for the study period captured, so only those at high risk were referred. We assign this risk using the Criteria for FTLD Spectrum Disorder Pedigree Categorization, which was validated on a cohort of people with FTD syndromes.[24] High risk was defined as individuals with a family history of FTD and/or motor neuron disease (MND) and a known genetic variant, a family history of FTD and/or MND, or a strong family history of neurodegenerative disease. Final diagnoses were made once all investigations were completed.

Diagnoses were guided by contemporaneous international consensus criteria for bvFTD,[8] primary progressive aphasias,[25] Alzheimer disease/dementia,[26] progressive supranuclear palsy,[27] corticobasal degeneration,[28] dementia with Lewy bodies,[29] vascular cognitive impairment (NINDS-AIREN) with MRI changes of severe small vessel disease[30] and/or strokes, and recommendations for the bvFTD phenocopy syndrome[31] (Table 1). For this review, a phenocopy diagnosis was only made for those with an initial diagnosis of possible FTD after a minimum of 5 years of minimal/no change on cognitive and behavioral tests, negative MRI brain and FDG-PET imaging, and negative *C9orf72* expansion repeat expansions. Mean age of onset and symptom duration is listed in Table 2.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Eastern Health Research Ethics Committee (LR27-1213 15 February 2013). All data were fully anonymized before conducting the analyses for this study. The need to obtain participant consent was waived.

Statistical Methods

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26. Scores for the MMSE, ACE-R, and CBI-R (total and subsection scores) were computed. Chi-square tests or Fisher exact tests were conducted for categorical variables. ANOVA with post hoc tests were conducted to compare the clinical groups. Results were considered statistically significant if p was < 0.05, unless otherwise indicated.

Table 1 Frequency of Final Consensus Diagnosis

Final consensus diagnosis	Frequency of diagnosis, n (%)
Behavioral variant frontotemporal dementia	
a) bvFTD	43 (26.7)
b) FTD/MND	2 (1.2)
bvFTD phenocopy	5 (3.1)
Primary progressive aphasia	
a) Semantic dementia	10 (6.2)
b) Primary progressive aphasia not classifiable	3 (1.9)
Progressive supranuclear palsy	15 (9.3)
Corticobasal syndrome	2 (1.2)
Alzheimer disease	
a) Alzheimer dementia	16 (9.9)
b) Amnestic MCI	3 (1.9)
Vascular cognitive impairment	
a) VCI	17 (10.6)
b) Mixed VCI/AD	4 (2.5)
c) Vascular cognitive impairment/depression	1 (0.6)
Primary psychiatric disorder[a]	25 (15.5)
Other neurologic disorder[b]	10 (6.2)
Acquired brain injury	5 (3.1)
TOTAL	161

[a] Details of the primary psychiatric disorders are presented in eTable 1.
[b] Details of the other neurologic disorders are presented in eTable 2.

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary material.

Results

Over the study period (January 1, 2010, to December 31, 2019), 611 patients were referred with available data, of whom 161 (26.4%) fulfilled the prespecified FNI referral criteria. All participants identified as cisgender men or women in this cohort: 120 (75.5%) were men. The mean age at the time of clinic

Table 2 Demographic, Cognitive, and Comorbidity Data for Final Consensus Diagnoses

	bvFTD (n = 43)	PPD (n = 25)	VCI (n = 17)	AD (n = 16)	PSP (n 15)	SD (n = 10)	Phenocopy (n = 5)	TBI/ABI (n = 5)	CBS (n = 2)	F/χ^2	*p* Value
No. of men (%)	31 (72.1)	20 (80.0)	12 (70.6)	10 (62.5)	13 (86.7)	7 (70)	3 (60)	4 (80)	1 (50)	12.75	0.55
Mean age of presentation, y (SD)	63 (9.3)	59.7 (8.4)	66.4 (7.8)	72.6 (5.7)	70 (7.3)	66.4 (6.0)	63 (9.4)	68.6 (4.8)	64 (8.5)	3.46	<0.001
Mean age of symptom onset (SD)	58.4 (8.3)	56.6 (9.0)	62.8 (9.3)	68.3 (6.5)	66.7 (7.4)	61.7 (6.1)	58.6 (9.3)	63.6 (6.1)	62.0 (8.5)	3.33	<0.001
Mean symptom duration, years (SD)	4.9 (2.9)	3.2 (2.2)	3.6 (2.6)	3.9 (1.9)	3.5 (1.5)	4.7 (2.5)	4.4 (1.1)	5.0 (3.1)	2.0 (0.0)	2.06	0.017
Mean CCI score (SD)	3.7 (1.9)	2.4 (1.9)	4.6 (2.5)	5.5 (1.3)	4.6 (1.6)	3.7 (1.3)	3.4 (1.9)	4.4 (1.8)	3.0 (1.4)	3.99	<0.001
Mean MMSE (SD)	25.2 (3.7)	25.2 (5.5)	26.1 (1.2)	23.0 (3.8)	27.2 (1.3)	23.5 (7.6)	26.5 (2.6)	26.8 (1.3)	18	1.00	0.454
Mean ACE-R (SD)	75.5 (14.8)	79.5 (19.3)	79.9 (7.4)	67.0 (10.7)	81.4 (6.4)	59.1 (24.7)	79.5 (9.5)	81.3 (7.0)	46	1.99	0.034

Abbreviations: ABI = acquired brain injury; ACE-R = Addenbrooke's Cognitive Examination-Revised; AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; CBI-R = Cambridge Behavioural Inventory-Revised; CBS = corticobasal syndrome; CCI = Charlson Comorbidity Index; F = Fisher exact test; MMSE = Mini-Mental State Examination; PPD = primary psychiatric disorder; PSP = progressive supranuclear palsy; SD = semantic dementia; TBI = traumatic brain injury; VCI = vascular cognitive impairment.

presentation was 65.5 years (SD 9.1, range 42–82; Table 2). Initial referral sources included primary care physicians (n = 58, 36.0%), geriatricians (n = 42, 25.4%), neurologists (n = 41, 24.9%), psychiatrists (n = 7, 4.2%), geriatric memory services (n = 3, 1.8%), and other clinicians (n = 10, 6.1%).

Final Consensus Diagnosis

The largest final consensus diagnosis was possible, probable, or definite bvFTD for 43 patients (26.7%), with a further 2 (1.2%) receiving a diagnosis of bvFTD/MND (Table 1). The next most frequent diagnosis was a PPD (15.5%), followed by VCI (13.7%).

Baseline Patient Demographic Characteristics

Demographic and baseline cognitive data by final diagnosis are presented in Table 2. There was a significant main effect of age of onset on the patient's clinical diagnosis ($F(14, 146) = 3.33$, $p < 0.001$, $\eta_p^2 = 0.24$). In particular, patients diagnosed with frontal variant AD had a later age of symptom onset compared with patients with bvFTD ($t(57) = 4.29$, $p < 0.001$), and compared with patients diagnosed with semantic dementia ($t(24) = 2.55$, $p = 0.018$). Patients diagnosed with a PPD were younger at symptom onset than those with AD ($t(39) = 4.48$, $p < 0.001$). However, there were no significant differences in age of symptom onset between patients diagnosed with bvFTD and a PPD ($t(66) = 0.83$, $p = 0.41$). There was no significant association between clinical diagnoses and family history of dementia ($\chi^2(14) = 11.9$, $p = 0.61$).

Medical Comorbidities

A one-way between-subject ANOVA was conducted to compare the effect of CCI scores on clinical diagnosis. There was a significant effect of CCI on the diagnosis ($F(12, 146) = 2.35$, $p < 0.001$, $\eta_p^2 = 0.28$; Table 2). Post hoc analyses revealed that patients diagnosed with AD had a higher comorbidity score compared with those with bvFTD ($p < 0.001$), VCI ($p = 0.035$), and PPD ($p < 0.001$). In addition, patients diagnosed with bvFTD had higher CCI scores when compared with patients diagnosed with PPD ($p = 0.44$).

Cognitive Test Scores

There were no significant differences across the diagnostic groups on the MMSE ($F(13, 96) = 1.00$, $p = 0.45$, $\eta_p^2 = 0.12$; Table 2). One hundred five patients completed the ACE-R. There was a significant difference in the ACE-R total score across the diagnostic groups ($F(12, 92) = 1.99$, $p < 0.05$, $\eta_p^2 = 0.21$; Table 2). People diagnosed with AD had lower total scores compared with bvFTD, but this was not significant ($t(46) = -1.90$, $p = 0.064$). ACE-R total scores did not differentiate patients with bvFTD and PPD ($p = 0.44$).

Cambridge Behavioural Inventory-Revised

In total, 100 caregivers (61.1% of the cohort) completed the CBI-R questionnaire. The CBI-R total score did not distinguish the bvFTD group from the other diagnostic categories ($p = 0.25$). Mean scores from the CBI-R subsections were also compared across the diagnostic groups. Multivariate analyses revealed a significant effect on the eating behaviors subsection and diagnostic group ($F(15, 521.19) = 34.75$, $p < 0.05$). An independent samples *t*-test was conducted to examine the effect of mean total eating habit scores across different diagnostic groups. The findings revealed a higher mean total score for the bvFTD group relative to the VCI group ($t(38) = 3.77$, $p = 0.001$) and PPD ($t(43) = 3.22$, $p = 0.002$). Group differences on the stereotypic behaviors subsection trended toward significance ($p = 0.058$).

Psychiatric History

In total, 72 patients with FNI had a preexisting psychiatric diagnosis (44.7%). Table 3 summarizes the number of years patients held this preexisting diagnosis. A preexisting diagnosis was most prevalent in the FNI cohort for patients receiving a final consensus diagnosis of bvFTD (n = 14) and PPD (n = 15) (Table 4). For these latter 2 groups, there was no significant association between psychiatric history (years) and final consensus diagnosis ($\chi^2(4) = 8.71$, $p = 0.069$).

Table 4 Psychiatric History for the bvFTD and PPD Groups

Years of psychiatric history	bvFTD (n = 43) No. (%)	PPD (n = 25) No. (%)
0	29 (67.4)	11 (44)
<5	6 (14)	4 (16)
5–10	2 (4.6)	2 (8)
11–20	3 (7)	1 (4)
>20	3 (7)	7 (28)

Discussion

At our specialist cognitive neurology service, 26.4% of patient referrals were for the consideration of a potential FTD diagnosis. Forty-five percent of these patients had a final diagnosis of a FTD syndrome, with the remainder diagnosed with PPD, VCI, AD, and ongoing or delayed effects of traumatic or acquired brain injury. We did not find that psychiatric history discriminated between PPD and bvFTD but that the presence of medical comorbidities did. Demographic variables such as age and sex and standard cognitive screens also did not discriminate, but some items of our behavioral screen, the CBI-R, were helpful.

A broad spectrum of both neurologic and psychiatric disorders underlies frontal network dysfunction. FTD syndromes overall represented 45% of diagnoses with bvFTD commonest diagnosis but only accounted for 28% of diagnoses. Late age of onset (particularly symptom onset at more than 70 years) was important in considering an AD diagnosis. We note that it is estimated that around 10% of people with a pathologic diagnosis of FTLD can present with symptoms beginning after 65 years of age,[32] often given an antemortem diagnosis of AD.

Patients with bvFTD also had a *higher* frequency of medical comorbidities than patients with primary psychiatric disorders. Historically, medical comorbidities, particularly autoimmune and inflammatory illnesses, have been overlooked in people with FTD syndromes.[33] These associations have been borne out in genome-wide association studies where striking overlaps have been seen in genetic enrichment between canonical autoimmune disorders and FTD/MND.[34] While people with a final diagnosis of AD had the highest comorbidities, this may reflect their increasing age.

A preexisting psychiatric disorder was common in people receiving both a final diagnosis of bvFTD and a primary psychiatric diagnosis.[14] This may reflect psychiatric symptoms common in the early symptomatic period of bvFTD, especially in association with the *C9orf72* expansion.[35] These diagnostic challenges support existing recommendations[13] for people with possible bvFTD or where the phenocopy syndrome is a consideration. Most authors recommend a multidisciplinary approach with evaluation by a neurologist and psychiatrist, identification of a second informant-based history, genetic testing for determination of the *C9orf72* repeat number, and serial follow-up for the monitoring of disease progression.[13] Commonly used cognitive screening tools (i.e., MMSE, ACE-R) did not assist in distinguishing the diagnostic groups, with no significant differences observed in total scores for patients diagnosed with bvFTD and PPD.

Behavioral and emotional symptoms occurring in patients with bvFTD may not be captured by standard cognitive and functional scales used for dementias even in specialist services, highlighting the importance of performing a structured behavioral interview.[36] Many authors have emphasized the need for the inclusion of at least 1 test of social cognition, acknowledging their deficits.[13] The CBI-R has been shown to differentiate dementia diagnoses.[20] We found that the eating behaviors subsection of the CBI-R was positively associated with a diagnosis of bvFTD. Eating abnormalities are reported in up to 60% of patients with FTD and are one of the 6 core criteria for its clinical diagnosis.[8] Abnormal eating behaviors are most prominent in patients with bvFTD and semantic dementia.[37] Eating behavior abnormalities have been formally characterized in FTD subtypes using data extracted from the CBI-R. The abnormal eating behaviors in these patients were not limited to an increased appetite, with a

Table 3 Psychiatric History

Years of diagnosis	Number	Percentage
0	89	55.3
<5	20	12.4
5–10	10	6.3
11–20	8	4.9
>20	23	14.3
Total	161	100

Eleven of the 161 patients did not have years documented.

significantly higher intake of sugar and carbohydrates also observed.[37] Thus, clinicians should inquire about changes in eating habits, in particular, a preference for sweet foods or increased carbohydrate intake, fixed food preferences, an increase in appetite, or a decline in table manners.

Strengths of our study are the long study period, quaternary setting, and comprehensive clinical evaluation by a multidisciplinary team, enabling capture of some of the most diagnostically challenging cases. Referral bias to our specialist service meant that we had a greater percentage of FTD diagnoses. van Gils et al. reported that only 11% of their patients with young-onset dementia had FTD[38] while Fieldhouse et al. noted a higher proportion of patients with a bvFTD diagnosis in those older than 65 years.[39] We note that the percentage of patients with a definite, not probable, diagnosis of bvFTD declined from those aged in their 50s and early 60s (31.6% and 24.7%, respectively) to those aged in their late 60s (15.5%) to mid-70s (8.5%), raising the possibility of pathologies other than FTLD. Postmortem verification was only available in a small number of people who had consented for brain banking; misdiagnosis in our cohort may be problematic. However, the mean age of onset for our participants with bvFTD (58.4 ± 8.3 years) is consistent with previously reported cohorts.

Another weakness is that neuroimaging data were not quantitatively analyzed, although we note we have performed such correlates in other studies.[40] Race and ethnicity were not systematically recorded in our database (assigned sex and affirmed gender were) so could not be reported. We note this has been amended in the current version of our database. While we asked clinical questions—what is the final diagnosis of those referred with potential FTD?—we do not report on the referral questions of all those subsequently diagnosed with a FTD syndrome in our clinic. FDG-PET brain availability was good, but access to CSF biomarkers was limited, and blood-based biomarkers were only available through research participation. Amyloid PET imaging is readily accessed in Melbourne but is not covered by our universal health care (Medicare) and hence only available to those participants who could afford to pay.

Early and accurate diagnosis of FTD syndromes is important, to facilitate information provision and counseling to patient's caregivers and families, to allow for future planning, and to facilitate implementation of evidence-based supportive therapies. Neurofilament light chain in both CSF and plasma is a promising biomarker, demonstrating high accuracy in discriminating bvFTD and PPD.[41-43] Potential disease-modifying therapies will likely have greatest efficacy in the earliest stages of disease. The advent of better fluid biomarkers,[44,45] diagnostic checklists,[46] prospective clinical databases,[38] and learnings from international genetic FTD consortia[47-49] will also improve our diagnostic pathways.

TAKE-HOME POINTS

- Not all frontal network impairment is bvFTD; a range of neurodegenerative and primary psychiatric disorders may present with behavioral changes.
- FTD syndromes were diagnosed in 45% of those referred to a specialist cognitive neurology service—bvFTD was the final diagnosis in over a quarter.
- Common cognitive screens, psychiatric history, and the presence of medical comorbidities may not assist in distinguishing bvFTD from other diagnoses, but behavioral screens might.
- Structured behavioral informant interviews should include questions about the presence of abnormal eating behaviors.
- Genetic referral for determination of *C9orf72* repeat expansions is important for early FTD diagnosis in cases of high suspicion and low clinical certainty.

Medical and psychiatric comorbidities can both complicate and contribute to the diagnosis. Structured behavioral interviews, including features such as eating abnormalities, may be clinically informative. The advent of plasma biomarkers and better access to molecular imaging will improve our diagnostic accuracy.

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References

1. Lough S, Gregory C, Hodges JR. Dissociation of social cognition and executive function in frontal variant frontotemporal dementia. *Neurocase*. 2001;7(2):123-130. doi:10.1093/neucas/7.2.123
2. Strikwerda-Brown C, Ramanan S, Irish M. Neurocognitive mechanisms of theory of mind impairment in neurodegeneration: a transdiagnostic approach. *Neuropsychiatr Dis Treat*. 2019;15:557-573. doi:10.2147/NDT.S158996
3. Boeve BF, Boxer AL, Kumfor F, Pijnenburg Y, Rohrer JD. Advances and controversies in frontotemporal dementia: diagnosis, biomarkers, and therapeutic considerations. *Lancet Neurol*. 2022;21(3):258-272. doi:10.1016/S1474-4422(21)00341-0
4. Hendriks S, Peetoom K, Bakker C, et al. Global prevalence of young-onset dementia: a systematic review and meta-analysis. *JAMA Neurol*. 2021;78(9):1080-1090. doi:10.1001/jamaneurol.2021.2161
5. Singleton EH, Pijnenburg YAL, Sudre CH, et al. Investigating the clinico-anatomical dissociation in the behavioral variant of Alzheimer disease. *Alzheimers Res Ther*. 2020;12(1):148. doi:10.1186/s13195-020-00717-z
6. Devenney E, Swinn T, Mioshi E, et al. The behavioural variant frontotemporal dementia phenocopy syndrome is a distinct entity - evidence from a longitudinal study. *BMC Neurol*. 2018;18(1):56. doi:10.1186/s12883-018-1060-1
7. 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. doi:10.1097/WCO.0b013e3283404309
8. 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. doi:10.1093/brain/awr179
9. Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. *Brain*. 1992;115(Pt 6):1783-1806. doi:10.1093/brain/115.6.1783
10. Barker MS, Dodge SG, Niehoff D, et al. Living with frontotemporal degeneration: diagnostic Journey, symptom experiences, and disease impact. *J Geriatr Psychiatry Neurol*. 2023;36(3):201-214. doi:10.1177/08919887221119976
11. Chow TW, Pio FJ, Rockwood K. An international needs assessment of caregivers for frontotemporal dementia. *Can J Neurol Sci*. 2011;38(5):753-757. doi:10.1017/s0317167100054147
12. Sejourne C, Dworkin JD, Barker MS, et al. Demographic and symptom correlates of initial Idiopathic psychiatric diagnosis in frontotemporal dementia. *J Geriatr Psychiatry Neurol*. 2023;36(3):193-200. doi:10.1177/08919887221130267
13. Ducharme S, Dols A, Laforce R, et al. Recommendations to distinguish behavioural variant frontotemporal dementia from psychiatric disorders. *Brain*. 2020;143(6):1632-1650. doi:10.1093/brain/awaa018
14. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. 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. doi:10.4088/JCP.10m06382oli
15. Krudop WA, Dols A, Kerssens CJ, et al. The pitfall of behavioral variant frontotemporal dementia mimics despite multidisciplinary application of the FTDC criteria. *J Alzheimers Dis*. 2017;60(3):959-975. doi:10.3233/JAD-170608
16. Vijverberg EG, Wattjes MP, Dols A, et al. Diagnostic accuracy of MRI and additional [18F]FDG-PET for behavioral variant frontotemporal dementia in patients with late onset behavioral changes. *J Alzheimers Dis*. 2016;53(4):1287-1297. doi:10.3233/JAD-160285

17. Pose M, Cetkovich M, Gleichgerrcht E, Ibáñez A, Torralva T, Manes F. The overlap of symptomatic dimensions between frontotemporal dementia and several psychiatric disorders that appear in late adulthood. *Int Rev Psychiatry*. 2013;25(2):159-167. doi:10.3109/09540261.2013.769939
18. Brodtmann A, Cowie T, McLean C, Darby D. Phenocopy or variant: a longitudinal study of very slowly progressive frontotemporal dementia. *BMJ Case Rep.* 2013;2013:bcr2012008077. doi:10.1136/bcr-2012-008077
19. Vassar M, Holzmann M. The retrospective chart review: important methodological considerations. *J Educ Eval Health Prof.* 2013;10:12. doi:10.3352/jeehp.2013.10.12
20. Wear HJ, Wedderburn CJ, Mioshi E, et al. The cambridge behavioural inventory revised. *Dement Neuropsychol.* 2008;2:102-107. doi:10.1590/S1980-57642009DN20200005
21. 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. doi:10.1016/0022-3956(75)90026-6
22. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry*. 2006;21(11):1078-1085. doi:10.1002/gps.1610
23. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47(11):1245-1251. doi:10.1016/0895-4356(94)90129-5
24. Wood EM, Falcone D, Suh E, et al. Development and validation of pedigree classification criteria for frontotemporal lobar degeneration. *JAMA Neurol.* 2013;70(11):1411-1417. doi:10.1001/jamaneurol.2013.3956
25. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology* 2011;76(11):1006-1014. doi:10.1212/WNL.0b013e31821103e6
26. 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. doi:10.1016/j.jalz.2011.03.005
27. Höglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov Disord.* 2017;32(6):853-864. doi:10.1002/mds.26987
28. Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. *Neurology*. 2013;80(5):496-503. doi:10.1212/WNL.0b013e31827f0fd1
29. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology*. 2017;89(1):88-100. doi:10.1212/WNL.0000000000004058
30. Duering M, Biessels GJ, Brodtmann A, et al. Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol.* 2023;22(7):602-618. doi:10.1016/S1474-4422(23)00131-X
31. Piguet O, Hodges JR. Behavioural-variant frontotemporal dementia: an update. *Dement Neuropsychol.* 2013;7(1):10-18. doi:10.1590/S1980-57642013DN70100003
32. Seo SW, Thibodeau MP, Perry DC, et al. Early vs late age at onset frontotemporal dementia and frontotemporal lobar degeneration. *Neurology*. 2018;90(12):e1047-e1056. doi:10.1212/WNL.0000000000005163
33. Miller ZA, Rankin KP, Graff-Radford NR, et al. TDP-43 frontotemporal lobar degeneration and autoimmune disease. *J Neurol Neurosurg Psychiatry*. 2013;84(9):956-962. doi:10.1136/jnnp-2012-304644
34. Broce I, Karch CM, Wen N, et al. Immune-related genetic enrichment in frontotemporal dementia: an analysis of genome-wide association studies. *PLoS Med.* 2018;15(1):e1002487. doi:10.1371/journal.pmed.1002487
35. Solje E, Aaltokallio H, Koivumaa-Honkanen H, et al. The phenotype of the C9ORF72 expansion carriers according to revised criteria for bvFTD. *PLoS One*. 2015;10(7):e0131817. doi:10.1371/journal.pone.0131817
36. Fieldhouse JLP, van Dijk G, Gillissen F, et al. A caregiver's perspective on clinically relevant symptoms in behavioural variant frontotemporal dementia: tools for disease management and trial design. *Psychogeriatrics*. 2023;23(1):11-22. doi:10.1111/psyg.12898
37. Ahmed RM, Irish M, Kam J, et al. Quantifying the eating abnormalities in frontotemporal dementia. *JAMA Neurol.* 2014;71(12):1540-1546. doi:10.1001/jamaneurol.2014.1931
38. van Gils AM, Rhodius-Meester HFM, Leeuwis AE, et al. Young-onset dementia in memory clinics in The Netherlands: study design and description of PRE-CODE-GP. *Alzheimers Dement (Amst)*. 2023;15(3):e12471. doi:10.1002/dad2.12471
39. Fieldhouse JLP, Gossink FT, Feenstra TC, et al. Clinical phenotypes of behavioral variant frontotemporal dementia by age at onset. *J Alzheimers Dis.* 2021;82(1):381-390. doi:10.3233/JAD-210179
40. Vogel AP, Poole ML, Pemberton H, et al. Motor speech signature of behavioral variant frontotemporal dementia: refining the phenotype. *Neurology*. 2017;89(8):837-844. doi:10.1212/WNL.0000000000004248
41. Eratne D, Loi SM, Walia N, et al. A pilot study of the utility of cerebrospinal fluid neurofilament light chain in differentiating neurodegenerative from psychiatric disorders: a 'C-reactive protein' for psychiatrists and neurologists? *Aust N Z J Psychiatry*. 2020;54(1):57-67. doi:10.1177/0004867419857811
42. Katisko K, Cajanus A, Jääskeläinen O, et al. Serum neurofilament light chain is a discriminative biomarker between frontotemporal lobar degeneration and primary psychiatric disorders. *J Neurol.* 2020;267(1):162-167. doi:10.1007/s00415-019-09567-8
43. Vijverberg EG, Dols A, Krudop WA, et al. Cerebrospinal fluid biomarker examination as a tool to discriminate behavioral variant frontotemporal dementia from primary psychiatric disorders. *Alzheimers Dement (Amst).* 2017;7:99-106. doi:10.1016/j.dadm.2017.01.009
44. Ooi S, Patel SK, Eratne D, et al. Plasma neurofilament light chain and clinical diagnosis in frontotemporal dementia syndromes. *J Alzheimers Dis.* 2022;89(4):1221-1231. doi:10.3233/JAD-220272
45. van der Ende EL, Meeter LH, Poos JM, et al. Serum neurofilament light chain in genetic frontotemporal dementia: a longitudinal, multicentre cohort study. *Lancet Neurol.* 2019;18(12):1103-1111. doi:10.1016/S1474-4422(19)30354-0
46. Ducharme S, Pearl-Dowler L, Gossink F, et al. The frontotemporal dementia versus primary psychiatric disorder (FTD versus PPD) checklist: a bedside clinical tool to identify behavioral variant FTD in patients with late-onset behavioral changes. *J Alzheimers Dis.* 2019;67(1):113-124. doi:10.3233/JAD-180839
47. Moore KM, Nicholas J, Grossman M, et al. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. *Lancet Neurol.* 2020;19(2):145-156. doi:10.1016/S1474-4422(19)30394-1
48. Asken BM, Ljubenkov PA, Staffaroni AM, et al. Plasma inflammation for predicting phenotypic conversion and clinical progression of autosomal dominant frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry*. 2023;94(7):541-549. doi:10.1136/jnnp-2022-330866
49. Staffaroni AM, Quintana M, Wendelberger B, et al. Temporal order of clinical and biomarker changes in familial frontotemporal dementia. *Nat Med.* 2022;28(10):2194-2206. doi:10.1038/s41591-022-01942-9

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