The Diagnostic Landscape of Behavioral Variant Frontotemporal Dementia

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ABSTRACT

The behavioral variant of frontotemporal dementia (bvFTD) is a progressive, neurodegenerative disorder, characterized by profound changes in personality, behavior, and social comportment. Diagnosis of bvFTD is challenging, and it is frequently misdiagnosed as an idiopathic psychiatric disorder (e.g., major depressive disorder, bipolar disorder) or another neurodegenerative disease (e.g., Alzheimer's disease dementia). The diagnostic challenge is exacerbated by a lack of reliable in vivo biological markers of disease pathology, which means that, at present, diagnosis relies largely on detailed behavioral and cognitive assessments. In this article, we discuss how clinical diagnostic criteria for bvFTD have evolved over the past three decades, and emphasize the diagnostic uncertainty that can arise when trying to distinguish between bvFTD and primary psychiatric disorders or other neurodegenerative diseases. In highlighting the strengths and limitations of the revised diagnostic criteria, and taking into account current diagnostic predicaments, we provide evidence-based recommendations for clinicians facing this diagnostic question. Finally, we touch on the importance of early (i.e., prodromal) diagnosis, and explain the utility of biomarkers for bvFTD diagnosis, with a nod to exciting research developments in this area.

KEYWORDS: behavioral variant frontotemporal dementia; frontotemporal lobar degeneration; diagnosis; diagnostic uncertainty

GENERAL INTRODUCTION

Frontotemporal dementia (FTD) is the clinical diagnosis most commonly associated with frontotemporal lobar degeneration (FTLD) neuropathology. FTD is a progressive, neurodegenerative disorder with an insidious onset. Based on the initial predominant symptoms, FTD can present as the behavioral variant (bvFTD), or as a language-based disorder, known as primary progressive aphasia (PPA). Of the FTD phenotypes, bvFTD is the most common.[1,2] Considered an "early-onset" dementia, the typical age of symptom onset is between 45–65 years. Survival is highly variable and differs among FTD phenotypes, but for bvFTD, the average survival from symptom onset is estimated to be between four–eight years.[3,4] Approximately 30–50% of patients with FTD will have a strong family history of dementia, and 10–20% will show an autosomal dominant inheritance pattern, with pathogenic variants of the *MAPT, GRN* and *C9orf72* genes accounting for the majority of these cases.[5]

BvFTD, the behavioral variant, is characterized by marked changes in personality and social conduct. It is the prototypical "frontal lobe" dementia, with severe apathetic and disinhibited behavior being two of its hallmark symptoms. Patients tend to show reduced motivation, decreased interest in hobbies and social engagements, a lack of concern for themselves or family members, poor social decorum, risk-taking behavior, repetitive or ritualistic behaviors such as tapping or counting, and binge eating, or an increased preference for sweet food. Cognitively, problems with executive function, such as complex problem solving and planning, are key. On neuroimaging, gross frontal and temporal lobe atrophy is often present, and on neuropathological examination, patients with bvFTD will most commonly show aggregated tau or TDP-43 proteinopathies.

DIAGNOSTIC CRITERIA

The first attempt at reifying clinical diagnostic criteria for FTD was published in a consensus statement from the Lund and Manchester groups in 1994.[6] The core diagnostic features put forth in this paper were extensive, including 10 "behavioral disorder" symptoms, as well as additional affective, speech-related, and physical symptoms, and a lengthy list of 16 exclusion features. Just four years later, in 1998, an updated version of these criteria were published by Neary and colleagues.[7] The Neary et al criteria separated out the FTD phenotypes into a behavioral variant and two language variants, and these diagnostic criteria were quickly adopted by most dementia centers. According to Neary et al, the behavioral syndrome, simply referred to as "FTD," could be considered a disorder of character change and disordered social conduct. Their core features included declines in social interpersonal conduct and in regulation of personal conduct, emotional blunting, and loss of insight, with insidious onset and gradual progression. Supportive diagnostic features included six additional behavioral symptoms, as well as speech/language changes and physical signs. The Neary et al criteria represented an important step forward

in the diagnosis of the behavioral syndrome of FTD, which would later come to be known as bvFTD. However, the limitations of these diagnostic criteria became apparent as the field advanced; primarily, they were criticized for being overly restrictive since all core features had to be present for a diagnosis, and were not well suited to detect impairments at the early stages of disease.

Designed to address these limitations, the most recent consensus criteria for bvFTD were published in 2011 by the International Behavioral Variant FTD Criteria Consortium, informally known as the Rascovsky et al criteria.[8] These criteria include six core features: 1) behavioral disinhibition, 2) apathy or inertia, 3) loss of sympathy or empathy, 4) perseverative, stereotyped, or compulsive/ritualistic behavior, 5) hyperorality or dietary changes, and 6) executive dysfunction with relative sparing of episodic memory and visuospatial functions.[8] For a diagnosis of "possible bvFTD," the individual must have three of the six symptoms present, and the symptoms must show progressive deterioration. For a diagnosis of "probable bvFTD," the individual must additionally have functional decline and evidence of frontal and/or anterior temporal disruption on neuroimaging. "Definite bvFTD" requires histopathological evidence of FTLD or a known pathogenic mutation to be present.

The Rascovsky et al criteria were developed based on explicitly observable symptoms, with the aim to minimize ambiguity and improve inter-rater reliability. This was posited as an advantage over the previous sets of diagnostic criteria, which had included terms that were clinically ambiguous (e.g., "impaired regulation of personal conduct") and required assumptions about the patient's cognitive/emotional state to be made (e.g., loss of insight). The Rascovsky et al approach was also the first data-driven method to develop diagnostic criteria, as the authors conducted a retrospective review of cases with confirmed FTLD pathology on autopsy to define the core characteristics of the bvFTD syndrome. Compared to the 1998 criteria, the 2011 criteria had significantly improved sensitivity – that is, they captured more true cases – at the expense of specificity. However, in relaxing the requirements for diagnosis, there is the potential for more false positive diagnoses, or misdiagnoses.

DIAGNOSTIC UNCERTAINTY

Diagnosis of bvFTD is challenging, as the core impairments are behavioral and overlap with the symptoms of psychiatric and other neurodegenerative disorders. This challenge is intensified by the fact that diagnoses are still primarily clinical; that is, without accurate confirmatory biological markers (biomarkers) of the disease, which we discuss later in this article; bvFTD diagnosis relies almost exclusively on behavioral and cognitive assessment.[9] Despite the multiple attempts at optimizing the diagnosis of bvFTD, misdiagnosis is a common and ongoing issue, which is a stressful experience for patients and families. Indeed, in one survey-based study, more than half of bvFTD patients had to see three or more doctors for a diagnosis to be made.[10] A recent retrospective review of records of patients admitted to an inpatient psychiatric service in Australia found that, compared to other neurodegenerative diagnoses, bvFTD was the most unstable diagnosis.[11] Specifically, almost half of patients who were given a diagnosis of bvFTD had their diagnosis switched at some point.[11] Other research has reported misdiagnosis rates of 25–50%.[10,12,13]

BvFTD is most frequently misdiagnosed as a primary psychiatric disorder, commonly major depression, bipolar disorder, schizophrenia, and anxiety.[12,13] This is unsurprising given the significant overlap in symptoms such as avolition, social withdrawal, risk-taking behavior, and, in some cases, delusions and hallucinations. A key challenge, and flourishing research area, is differentiating bvFTD from primary psychiatric disorders.

Primary Psychiatric Disorders

Despite some evidence suggesting that poorer global cognition and letter fluency scores are more indicative of bvFTD,[14] at mild stages, cognitive testing has not proven particularly helpful in distinguishing bvFTD from primary psychiatric disorders. Tests of social cognition have also shown some promise and may become more important in clinical practice in future years.[9] While social cognition deficits can be present in psychiatric disorders such as depression, schizophrenia, and bipolar disorder, the impairments are usually more profound in bvFTD.[15] One study found that tasks of emotion recognition (e.g., Ekman faces) can differentiate bvFTD from other major psychiatric disorders,[16] but research directly comparing bvFTD to specific psychiatric disorders is lacking.

Psychiatric interview tools, such as the Neuropsychiatric Inventory (NPI),[17] help to characterize psychiatric symptoms in dementia, but are not sufficient to exclude a diagnosis of a primary psychiatric disorder.[9] Instead, careful and detailed clinical phenotyping, including phenomenological descriptions of symptoms that may have important diagnostic value, is needed.[9] One example of this is apathy. Apathetic behavior, such as watching television all day, which is commonly reported by bvFTD patients, may signal a diagnosis of major depression; however, in bvFTD the apathy lacks the concomitant feelings of sadness or hopelessness characteristic of depression.[18]

In current practice, the most reliable way to distinguish bvFTD from idiopathic psychiatric disorders is by monitoring symptom progression. Generally, psychiatric disorders will show stability or even improvement over time, whereas in bvFTD symptoms are progressive. However, this is complicated by the high incidence of mid-life dementia in schizophrenia,[19] as well as logistic factors (e.g., inconsistent access to a specialist clinician to monitor symptoms). Thus,

developing assessment tools to differentiate bvFTD from psychiatric disorders is essential.

Recently, there have been important advancements in this arena. Ducharme and colleagues identified 17 clinical features that are more strongly associated with either primary psychiatric disorders or bvFTD, and created a bedside checklist with an impressive discriminatory ability.[20] The checklist includes items such as "was the patient self-referred?" which are more likely in psychiatric disorders, as well as symptoms more common in neurodegeneration, such as, "are there abnormalities on elemental neurological examination?" A score ≥11 is indicative of bvFTD, with specificity over 93%, while scores ≤8 are indicative of a psychiatric disorder, with specificity higher than 91%.[20] Prospective studies comparing the checklist features between bvFTD and psychiatric disorders are ongoing.[21]

It is critical to highlight the nature of the clinical features in this checklist. Of the 17 features, seven of them relate to the patient's insight into or understanding of the situation, ("Is the patient aware of or concerned about cognitive or behavioral changes?") or blunted/distressed emotional responses ("Is the patient emotionally distressed by the current situation?"). Loss of insight and emotional blunting were two core features of the 1998 Neary et al diagnostic criteria,[7] but were removed in the 2011 Rascovsky et al revision,[8] due to the focus on overtly observable symptoms. Based on the work by Ducharme et al,[9,20] it appears as though these two symptoms may in fact be some of the most valuable features to discriminate bvFTD from primary psychiatric disorders, and could be at the center of why Rascovky et al do not discriminate well between bvFTD and primary psychiatric disorders.[22] Future research should focus on reintegrating these features into the diagnostic criteria for bvFTD, and improving measurement of these somewhat nebulous symptoms.

Phenocopy Syndrome

The relative stability of psychiatric disorders vs. the progressive nature of bvFTD in distinguishing the two is further complicated by the bvFTD "phenocopy syndrome." A portion of patients meet clinical criteria for bvFTD but do not have evidence of FTD on imaging and do not decline functionally.[23] It has been proposed that this represents a bvFTD "phenocopy syndrome." Some suggest that this is a psychiatric disorder rather than true bvFTD, as at least a portion of patients with this phenocopy syndrome do not have FTLD neuropathology on autopsy.[24] Nevertheless, there are reports of the bvFTD phenocopy syndrome in carriers of the *C9orf72* pathogenic expansion, who would be expected to have FTLD pathology given their genetic status.[23,25] It remains unclear whether the phenocopy syndrome represents a psychiatric disorder or belongs on the bvFTD spectrum, and currently the only way to ascertain whether a patient has true or phenocopy bvFTD is to monitor them longitudinally.

Other Neurodegenerative Disorders

When distinguishing bvFTD from other neurodegenerative disorders, the two most common differential diagnoses are early-onset Alzheimer's disease (AD) and dementia with Lewy Bodies (DLB), which can also occur in those younger than 65 years. Poor insight is not as useful in parsing out these neurodegenerative diagnoses from each other as it is in the psychiatric disorder vs. bvFTD differential diagnosis, as it may be present in other dementias.[26,27] Cognitively there is significant overlap, as executive dysfunction is common across dementias; however, executive impairments tend to be more severe in bvFTD,[28] and some executive function tests are better at discriminating bvFTD from AD than others.[29] Traditionally, poor performance on episodic memory testing would be suggestive of AD, and indeed impaired episodic memory has typically been viewed as incongruent with bvFTD, but mounting evidence of episodic memory impairments in bvFTD has challenged this.[30–32] Neuropsychiatric symptoms, such as apathy, are often present in other neurodegenerative disorders, and characteristic features of DLB, such as psychosis and parkinsonism, have been observed in bvFTD.

Perhaps the most difficult neurodegenerative diagnosis to clinically differentiate from bvFTD is the behavioral variant of Alzheimer's disease (bvAD). BvAD is a rare, non-amnestic form of AD, where prominent behavioral problems are caused by Alzheimer pathology. The first diagnostic criteria for the clinical syndrome of bvAD were published recently,[33] and all five of the Rascovsky et al bvFTD behavioral features are represented in the core bvAD phenotype. There are, however, some very subtle clinical differences; for example, on average, patients with bvAD exhibit milder behavioral impairments than bvFTD patients at a similar disease stage, including less compulsivity and hyperorality.[33] One recent study showed more significant visuospatial impairments in bvAD compared to bvFTD,[34] but direct comparison studies are lacking. Currently, the only way to distinguish bvAD from bvFTD is by the presence of AD biomarkers (e.g. β-amyloid pathology in CSF or PET) or known pathogenic genetic variants.

PRODROMAL DIAGNOSIS

An important issue for all neurodegenerative diseases, which has recently gained traction in the bvFTD field, is that of early or "prodromal" diagnosis. The disease prodrome is the phase when mild symptoms are present, before the disease becomes fully manifest. This is a critical stage, as it is the phase during which interventions are likely to be most effective, and clinical trials would seek to enroll participants. In AD, this phase is known as Mild Cognitive Impairment (MCI). In FTD, various research groups have tackled the question of prodromal diagnosis in different ways.

At the earliest stages of disease, when symptoms are mild and have large overlap with normal populations, the

trade-off between sensitivity and specificity becomes paramount. High sensitivity means that there is a low bar for diagnosis, and therefore most cases are captured, but there is a risk of false positives. High specificity means that the requirements for diagnosis are stricter, so false positive diagnoses are minimized, but there is a risk of missing true cases. In developing criteria for the diagnosis of prodromal FTD, most research groups have prioritized sensitivity. Criteria by Benatar et al to diagnose FTD in the context of motor neuron disease[35] only require one or two cognitive tests to be impaired for a diagnosis. Benussi et al cast a broad net of many neuropsychiatric, cognitive, and motor symptoms for prodromal diagnosis, but did not include any clinical control groups against which to compare their results.[36] Barker et al published the only criteria to diagnose the prodrome of the behavioral variant, rather than any variant, of FTD,[18] and found good specificity against an AD control group. Importantly, the priorities of this trade-off differ, depending on the circumstances; for example; a clinical trial for a high-risk drug may require excellent specificity, so that individuals without the disease are not inadvertently enrolled, whereas a yoga intervention could afford to enroll as many participants as possible as the risk is low, so high sensitivity would be key. But this flexibility needs to be weighed against the complexity of using several different sets of criteria for prodromal bvFTD. The development of in vivo FTLD biomarkers will be important for accurate early diagnosis.

BIOMARKERS

Currently, the diagnosis of bvFTD is hampered by the absence of specific in vivo biomarkers for the two most common FTLD pathologies, intraneuronal insoluble aggregates of either the tau or TDP-43 proteins (the exception to this is when a specific autosomal dominant genetic mutation is present, as this directly implicates a specific FTLD – either tau or TDP-43 – pathology). More commonly, neuroimaging can aid diagnostic confidence by examining gross neuroanatomic changes. A pattern of focal frontal and/or anterior temporal gray matter atrophy is characteristic of bvFTD, while FDG-PET or SPECT scans are used to identify hypometabolism in these same areas, which may be detectable prior to gray matter atrophy.[37] These imaging findings warrant a diagnosis of probable (rather than possible) bvFTD according to Rascovsky et al criteria,[8] but each modality has its limitations. MRI findings have good specificity but are not very sensitive, as it is not uncommon for mildly impaired patients to not exhibit atrophy by visual inspection.[38] FDG-PET or SPECT are more sensitive, but other syndromes, including psychiatric disorders, can be associated with diffuse or frontal hypometabolism.[38] Findings of global atrophy or hypometabolism on MRI and PET/SPECT, respectively, can be consistent with bvFTD as well as with AD or other forms of dementia. There are efforts underway to use machine learning to increase the diagnostic power of imaging exams.[39]

Testing for AD biomarkers, through amyloid PET scans and CSF amyloid or CSF hyperphosphorylated tau, has been a mainstay of research centers and some clinics to rule out the involvement of AD pathology in an apparent bvFTD syndrome. Accurate and less burdensome blood-based biomarkers of AD have been developed recently and are poised to become more widely used.[40] While not yet in routine clinical use, researchers have also identified neurofilament light chain (NfL) as a potential biomarker of FTLD. NfL is a protein marker of axonal injury and neuronal loss that is detected across many neurodegenerative disorders.[41] Emerging evidence suggests a potential utility in cases where a differential diagnosis of bvFTD vs. a primary psychiatric disorder is being considered, but is likely of lower utility to distinguish FTLD from other neurodegenerative illnesses.[42] Exciting work to identify even more specific blood-based biomarkers particular to tau and TDP-43 pathologies is in progress, including through examinations of proteins present in plasma extracellular vesicles.[43]

CONCLUSION

The diagnostic landscape of bvFTD is complex, compounded by a general lack of understanding of the disorder within the medical and broader community. The diagnostic criteria have undergone several revisions, generally moving from strict to more liberal, and with a focus on observable symptoms rather than internal states of the patient, with the benefit of higher rates of diagnosis but the downside of more false diagnoses. Future research should consider revising the criteria to re-introduce specific symptoms that show good diagnostic value but were removed in the most recent iteration, such as emotional blunting. Until accurate in vivo biomarkers become available, diagnosing bvFTD is challenging and requires a multidisciplinary effort and multifaceted assessment, including detailed phenotyping and phenomenological descriptions of behavioral symptoms.

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