Diagnostic Criteria for the Behavioral Variant of Frontotemporal Dementia (bvFTD): Current Limitations and Future Directions

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Abstract: The most widely established diagnostic criteria for the behavioral variant of frontotemporal dementia have now been in use for almost a decade. Although consensus criteria have provided a much needed standard for frontotemporal dementia research, a growing body of evidence suggests that revisions are needed to improve their applicability. In this article, we discuss the limitations of current diagnostic criteria and propose the establishment of an international consortium to revise diagnostic and research criteria for the behavioral variant of frontotemporal dementia.

Key Words: frontotemporal dementia, behavioral variant, diagnostic criteria, differential diagnosis, international consortium

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The behavioral variant of frontotemporal dementia (bvFTD) is a clinical syndrome characterized by progressive deterioration of behavior and cognition associated with prominent frontal, insular, and temporal lobar atrophy. Despite recent advances in the clinical characterization of bvFTD, its differentiation from Alzheimer disease (AD) can be problematic during life.[1,2] Both disorders produce a progressive dementia syndrome that can include executive dysfunction and behavior change, although these abnormalities are more characteristic of early bvFTD than AD. Accurate differential diagnosis of bvFTD is critical, as it has implications for heritability,[3–10] prognosis,[11–13] therapeutics,[14–18] and environmental management of patients.[19–22]

Three sets of bvFTD diagnostic criteria have been published since 1994[23–25] and reflect our evolving knowledge about the presentation and progression of the disease. These criteria have struggled to accommodate the demands of research while remaining clinically relevant. We assert that, on the basis of new information regarding bvFTD, it is time to revise bvFTD criteria to improve their relevance for clinicians and to achieve comparability between research groups. This article provides an historical overview of diagnostic criteria for bvFTD and proposes the establishment of an international consortium to revise diagnostic and research criteria for bvFTD.

DIAGNOSTIC CRITERIA—HISTORICAL BACKGROUND

In the 1980s, research groups in Lund, Sweden[26,27] and Manchester, UK,[28] began publishing large case series of patients with progressive focal frontal and anterior temporal lobe degeneration. Their joint experience culminated in 1994 with the first diagnostic and research criteria for this new neurodegenerative entity which they named frontotemporal dementia (FTD).[23] The Lund-Manchester Research Criteria specified core diagnostic, supportive, and exclusion features of FTD.

Core behavioral and affective symptoms included loss of insight, loss of personal and social awareness, disinhibition, mental rigidity, hyperorality, stereotyped behavior, utilization behaviors, distractibility, impulsivity, depression, hypochondriasis, emotional unconcern, and amimia. Progressive reduction of speech (ultimately leading to mutism) and profound failure on "frontal lobe" tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder were also consistent with an FTD diagnosis. Although representing an important first effort at definition, the Lund-Manchester criteria had several limitations. There was no mention of the relative importance of behavioral and other features to diagnosis (eg, whether they were necessary or sufficient or whether a specified number of features were needed to meet criteria for FTD). Furthermore, no operational definitions were provided, leaving the descriptive terms open to interpretation.

In 1998, Neary and colleagues[24] further refined the Lund-Manchester research criteria and renamed the frontotemporal spectrum of degenerative disorders as frontotemporal lobar degeneration (FTLD). The authors provided clinical descriptions of the 3 most common FTLD presentations: bvFTD; progressive nonfluent aphasia (PNFA),[29] and semantic dementia (SD).[30–33] The Neary criteria recognized the clinical heterogeneity within the FTLD spectrum and provided diagnostic guidelines for all 3 syndromes. Furthermore, they made a distinction between core and supportive diagnostic features—core features were made necessary for diagnosis whereas supportive features added weight to the diagnosis but were not required. Finally, the consensus criteria provided operational definitions and occasional examples for each diagnostic feature.

Recognizing that previous criteria for the spectrum of frontotemporal degenerations were primarily designed for research purposes, a third set of criteria was proposed by McKhann and colleagues.[25] These criteria aimed to enable clinicians to identify patients and expedite their referral for evaluation. The overall clinical spectrum was renamed FTD, and clinical criteria were simplified into 2 distinct presentations: (1) gradual and progressive changes in behavior, or (2) gradual and progressive changes in language function. Although a useful clinical heuristic, McKhann criteria lack sufficient specificity to be applicable for research purposes, particularly in the case of progressive aphasia syndromes (where SD and PNFA are collapsed into a general aphasic category).

A NOTE ON NOMENCLATURE

As the above review attests, the nosology of frontotemporal degenerations remains fluid and controversial. Considerable progress concerning the histochemistry, genetics, and clinical characterization of FTD has inevitably resulted in the proliferation of new terminology. Currently, most research groups favor the term FTD for the overall clinical syndrome, and frontotemporal degeneration to describe the overall pathological entity. We use the term bvFTD to designate a primarily behavioral presentation of the disorder, whereas the aphasic syndromes PNFA and SD have now been subsumed under the rubric of primary progressive aphasia. Finally, given the increased recognition of the clinical and pathologic overlap between FTD and movement disorders,[34–36] some authors propose a third, or "motor" branch of FTD, which includes FTD with motor neuron disease, corticobasal degeneration, and progressive supranuclear palsy (these last 2 disorders are sometimes also subsumed under the rubric of "tauopathies"). The present article will limit its scope to bvFTD.

LIMITATIONS OF NEARY CRITERIA FOR bvFTD

Since 1998, most dementia centers have adopted Neary criteria as the standard for bvFTD diagnosis. Over the years, some limitations of the consensus criteria have become apparent:

1. Large number of features: first, the large number of features makes them difficult to use in routine clinical practice. Current bvFTD criteria include 5 core features (insidious onset, early decline in social interpersonal conduct, early impairment in regulation of personal conduct, early loss of insight, and emotional blunting), and also 20 supportive, 11 exclusion, and 3 relative exclusion features. Rating of so many signs and symptoms proves burdensome even for the most experienced clinicians and researchers.
2. Restrictive in early stages of disease: recent evidence suggests that Neary criteria may be unduly restrictive, at least in the early stages of bvFTD. A study by Mendez and colleagues[37] revealed that, out of 53 patients who eventually met criteria for bvFTD, only 17 patients met all 5 core features at initial presentation. Most had early disengagement with poor insight, but more than half retained socially appropriate interpersonal conduct and emotional expression. Furthermore, whereas most bvFTD patients exhibit both disinhibition and apathy well into their disease course, patients may initially present as primarily disinhibited or primarily apathetic,[38] arguing for flexibility in the use of these core characteristics.
3. Limited role of supportive features: despite inclusion of 20 supportive features, these observations play no role in diagnostic classification. bvFTD patients must meet all core features, but the presence of supportive features does not favor or alter diagnosis in any practical manner and can sometimes be confusing or misleading. Recent evidence suggests that some supportive features (such as perseverative/stereotyped behavior and hyperorality), when present, may be particularly useful for diagnosis.[39–51] Unfortunately, the reliability of these supportive features has not yet been studied in a systematic way.
4. Features and disease course: qualifiers such as "early" and "late" are not defined, thus the time frame for manifestation of symptoms is open to interpretation.

Although features such as inertia and loss of empathy are common early in the disease course, features such as mutism, echolalia, and incontinence are seen only in advanced patients, and thus are unlikely to be helpful for early diagnosis.[38]

5. Level of diagnostic certainty: unlike the National Institute of Neurological and Communicative Disease and Stroke/Alzheimer Disease and Related Disorders criteria for AD, a basis for diagnosis of "probable" or "possible" FTD is absent, precluding examiners from qualifying their estimated level of diagnostic certainty.
6. Base rates: features such as echolalia and utilization behavior are uncommon and may offer no diagnostic value,[38,49] whereas features such as "low and labile blood pressure" or "normal EEG" may be incorrect.[52,53]
7. Ambiguity of behavioral terms: dementia research has focused primarily on cognitive and functional abilities that are easily testable and reliable. Although these symptoms are quite useful for the diagnosis of AD, they fail to capture the predominant behavioral symptoms of frontal lobe dysfunction. Many behavioral features included in the Neary criteria are subjective, and lack reliable scales to guide the user on items such as "emotional blunting" or "regulation of personal conduct." Findings from the California Non-AD Diagnostic Reliability Consortium suggest that the subjectivity of some items affect interrater reliability and the ultimate validity of these features.[54] Even when operationalized, names of diagnostic features should be self-explanatory for easy application (eg, clinicians may not realize that "loss of sympathy and empathy" is embedded within the feature "emotional blunting" unless they are familiar with the original consensus document).
8. Inference: although rating overt behavior may be relatively straightforward, interrater reliability declines when features require inference into a patient's cognitive or emotional state. Complex, multifactorial concepts such as "loss of insight" require not only inference, but determination of kind and quality of insight failure. A patient may state that he/she has bvFTD, but fail to appreciate the behavioral, functional, or cognitive consequences of his or her illness. In some cases, loss of insight into illness may be indistinguishable from lack of concern.[55–57]
9. Exclusion criteria: exclusion criteria such as "early and severe amnesia" and "spatial disorientation" may exclude a significant proportion of bvFTD patients. Some studies have documented the presence of marked anterograde amnesia as either the sole or dominant symptom in pathologically confirmed bvFTD cases,[58,59] whereas spatial disorientation (without mention of time course) may erroneously reject patients who are in the late stages of their illness.
10. Imaging and genetics: over the past 10 years, there have been significant advances in the identification of neuroimaging patterns[38,60–85] and pathogenic mutations[3–10] in bvFTD. New criteria should acknowledge the value of these features in the clinical diagnosis of the disorder.

NEW DIRECTIONS—REVISION OF DIAGNOSTIC CRITERIA FOR bvFTD

The past 9 years have seen considerable advances in the characterization and diagnosis of bvFTD. On the basis of the recent findings, we believe that both researchers and clinicians would benefit from revised and simplified bvFTD diagnostic criteria integrating the most salient clinical, genetic, and imaging characteristics of this disorder. Ideally, such criteria should: (1) significantly reduce the number of diagnostic features, (2) exclude arbitrary distinctions between core and supportive features, (3) allow greater flexibility in how patients can meet diagnostic criteria, (4) provide clearer operational definitions, (5) incorporate genetic and neuroimaging findings, and (6) distinguish between probable/possible or definite bvFTD, depending on the level of diagnostic certainty.

Stimulated by an National Institutes of Health-funded meeting focused on advancing better diagnostic approaches and treatments for bvFTD (Miami, 2006), we are in the process of establishing an international consortium to revise diagnostic and research criteria for this entity. The International bvFTD Criteria Consortium will include the most prominent researchers in the field of frontotemporal degeneration with the goal of developing new consensus criteria for bvFTD.

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