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Distinguishing Behavioral Variant Frontotemporal Dementia from Primary Psychiatric Disorders: A Review of Recently Published Consensus Recommendations from the Neuropsychiatric International Consortium for Frontotemporal Dementia

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Abstract

The behavioral variant of frontotemporal dementia (bvFTD) is the second-most common cause of dementia under the age of 65, but accurate diagnosis is often delayed for several years. While previous criteria have increased the ability of diagnosticians to distinguish between the behavioral variant of frontotemporal dementia (bvFTD) and other neurocognitive disorders such as Alzheimer's disease, distinguishing bvFTD from a primary psychiatric disorder (PPD) has been more challenging. Earlier this year, the Neuropsychiatric International Consortium for Frontotemporal Dementia published the first consensus recommendations to help clinicians distinguish between bvFTD and PPD. These recommendations were produced by a consortium of 45 scientists and clinicians from over 15 different countries, who explored aspects of history-taking, neuropsychological assessments, clinical scales, neuroimaging, CSF and serum biomarkers, and genetics. A multidisciplinary approach is encouraged throughout. Here we review those consensus recommendations and highlight use of novel tests and techniques. We also indicate where further research is needed, including methods to assess the dissemination and implementation of these recommendations. In this way, we encourage future efforts by clinicians and researchers alike to improve accurate recognition of bvFTD, thereby expanding opportunities for improved guidance and management.

Plain Language Summary:

Distinguishing between the behavioral variant of frontotemporal dementia (bvFTD) and primary psychiatric disorders (PPD) is challenging even for experienced specialist clinicians. In March of 2020, an international consortium published consensus recommendations to make this important distinction easier. This document offers guidance on history-taking, clinical scales,

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neuropsychological and physical examinations, tests of social cognition, neuroimaging, tests on blood and cerebrospinal fluid, and genetic testing.

Among other highlights, the consensus recommendations suggest a multidisciplinary approach integrating dedicated tests of social function with more commonly used neuropsychological assessments. Fluorodeoxyglucose-positron emission tomography (PET) scans and novel biomarkers such as neurofilament light (NFL) polypeptide may also be useful in especially challenging cases. We here comment about how to encourage dissemination and implementation of these consensus recommendations, as well as future directions of research to more firmly establish the clinical utility of the proposed diagnostic steps. Establishing measures of success, working with key stakeholders from diverse cultural and educational backgrounds to identify local challenges, and regularly revisiting and updating these recommendations will help ensure they remain relevant, practical, and impactful.

Keywords

frontotemporal dementia; guidelines; psychiatric disorders

Introduction:

The behavioral variant of frontotemporal dementia (bvFTD) is a neurodegenerative syndrome that presents with personality and behavior changes often considered “psychiatric” in nature, such as apathy, disinhibition, loss of empathy, new compulsive behaviors, hyperorality and executive dysfunction [1]. Many people with bvFTD are initially diagnosed with a primary psychiatric disorder (such as bipolar disorder or schizophrenia [2, 3]. Conversely, those with a primary psychiatric disorder are sometimes inaccurately diagnosed with bvFTD [4]. Accurate diagnosis is important for several reasons. The prognosis of a psychiatric disorder differs from that of an incurable progressive neurodegenerative condition and treatment options differ. A considerable proportion of bvFTD is inherited in an autosomal dominant fashion [5]. Patient and family counseling, then, will differ considerably between primary psychiatric disorders and bvFTD. Accurate and early diagnosis is also essential for enrollment in clinical research.

bvFTD is associated with underlying frontotemporal lobar degeneration, a histopathological diagnosis involving misfolding of tau, TAR-DNA binding protein 43, or Fused in Sarcoma (FUS) protein [5]. While biomarkers are increasingly available to assess for Alzheimer’s disease pathology, no specific biomarker is available for bvFTD. Diagnosis therefore depends primarily upon on clinical assessment. While current diagnostic criteria for bvFTD perform reasonably well in distinguishing underlying Alzheimer’s pathology from frontotemporal lobar degeneration, these criteria are less helpful for distinguishing FTD from primary psychiatric disorders [6].

Until recently, however, there was no standardized consensus on tools to guide practitioners attempts to distinguish primary psychiatric disorders from bvFTD. In response to this need, the Neuropsychiatric International Consortium for Frontotemporal Dementia (NIC-FTD) was established to develop consensus recommendations for best practices in the evaluation

of adults with new-onset behavioral changes in mid- and late- life that may be reflective of bvFTD.

We here review the main points of these consensus recommendations and discuss implications for their dissemination and implementation.

Summary of Consensus Recommendations:

Following PRISMA guidelines, the NIC-FTD used systematic review to determine level of evidence and establish consensus recommendations for various aspects of diagnostic evaluation of late-onset behavioral changes. This includes 1) patient history, including clinical scales, 2) psychiatric assessment, 3) physical and neurological examination findings, 4) bedside cognitive tests and neuropsychological examination, 5) tests of social cognition, 6) structural and nuclear imaging, 7) CSF and blood biomarkers, and 8) genetic testing. Each topic was assigned to NIC-FTD members, who then proposed minimal requirements, clinical recommendations, and further directions of research. Members then met to discuss recommendations, first in person and then over teleconferences and electronic surveys.

The authors emphasize the need for a careful history of symptom onset, corroborated by a knowledgeable caregiver. Risk factors such as traumatic brain injuries, earlier psychiatric disease, or learning disability should be explored. There are high rates of psychiatric disease in families with bvFTD, which could represent unrecognized neurodegeneration. A positive family history for psychiatric illness has been previously suggested to inappropriately bias diagnoses *away* from bvFTD [2], a potential pitfall about which a savvy diagnostician should be wary.

Use of clinical scales can reduce some of these cognitive biases among clinicians—however, few studies have examined how well FTD symptom scales distinguish bvFTD from primary psychiatric disorders. Examples of potentially useful scales for this purpose include the Frontal Behavioral Inventory's positive subscale[7], as well as the presence of aphasia, verbal apraxia [8], indifference, alien limb, and inappropriateness. Other potentially useful scales include DAPHNE, the Cambridge Behavioral Inventory (CBI), Stereotypy Rating Inventory (SRI), and the recently developed Frontotemporal Dementia versus Primary Psychiatric Disorder (FTD versus PPD) Checklist [8–11].

Psychiatrically, careful characterization of bvFTD patients has revealed that most do not fulfill formal DSM-5 criteria for any primary psychiatric disorder. Collaboration between a psychiatrist and neurologist may be helpful in diagnostically challenging cases. While a diagnosis of bvFTD may be more likely in the absence of the emotional distress that is often present in many types of primary psychiatric disorders, certain variants of bvFTD – for example, the *C9orf72* phenotype – can present slowly and with psychotic features that are diagnostically puzzling even for experienced subspecialists in this area [3].

The physical examination may offer clues towards underlying neurodegeneration, though is not absolute in either its sensitivity or specificity. Parkinsonism, for example, is common in FTD, but may also be present in those with primary psychiatric disorders who have received certain types of antipsychotics (i.e., those with potent dopamine type- 2 receptor antagonists)

as well as other psychotropics associated with medication- induced parkinsonism. Because bvFTD may entail motor neuron disease or movement disorders, the examiner should beware of signs pointing towards progressive supranuclear palsy, corticobasal syndrome, or amyotrophic lateral sclerosis. Classical “frontal release signs” (i.e., primitive reflexes) are part of the standard neurological examination and may reflect disturbances of neural networks affected in bvFTD, but they are of questionable utility as findings with which to distinguish bvFTD from primary psychiatric disorders given their common occurrence in both types of conditions [12–14].

No bedside cognitive screen has yet been able to clearly discriminate bvFTD from primary psychiatric disorders. While the reviewers postulate on the relative utility of different tools, most have only been shown to discriminate between different dementia subtypes, or focus more specifically on the executive dysfunction characteristic of bvFTD. Executive dysfunction, however, is highly non-specific for FTD versus primary psychiatric disorders. Tools such as the Frontal Assessment Battery, for example, which has some discriminative ability between FTD and Alzheimer’s disease, has no such ability between FTD and primary psychiatric disorders[7]. The ACE-III may have some utility in this regard, but has only been evaluated at later disease stages where diagnostic discrimination is generally easier [15].

More detailed neuropsychological assessments may again be useful in demonstrating executive dysfunction, but this dysfunction is also common in primary psychiatric disorders. Furthermore, executive dysfunction is not necessarily prominent in bvFTD. Neuropsychological assessments are best used longitudinally, then, to demonstrate decline, which would be more consistent with a neurodegenerative condition. While this method is diagnostically useful, however, it is necessarily time- demanding and not always available in a timely fashion in many clinical settings. Dedicated assessments of social cognition may be more informative [16]. Social cognition includes emotion recognition, theory of mind, moral reasoning, and empathy. However, these tests are often not included in standard neuropsychological assessment batteries, despite suggestions of efficacy.

Neuroimaging is already an essential component of bvFTD diagnosis, with the presence of frontal or anterior temporal atrophy or hypometabolism increasing certainty from “possible” to probable” in current criteria [1]. However, MRI may not be obviously abnormal in early stages or in certain variants of bvFTD such as the *C9orf72* phenotype [17]. While new analytic techniques may increase sensitivity in the future, normal brain imaging does not currently absolutely exclude FTLD pathology. Conversely, some primary psychiatric disorders may be associated with patterns of frontal hypometabolism on FDG-PET [18]. While a negative PET scan can reassure against neurodegenerative disease with a negative predictive value of up to 98% in one study [19], a positive PET with only small areas or non-specific patterns of hypometabolism does not necessarily rule out a primary psychiatric disorder [20].

CSF and serum biomarkers have less demonstrated utility at present, though markers such as neurofilament light chain (NfL) may soon point towards neuronal injury as a source of behavior changes [21], and should be considered if available. In CSF analysis of amyloid and tau, more commonly used to assess for Alzheimer’s pathology, a slightly elevated total tau

value may also suggest the presence of frontotemporal lobar degeneration when compared to controls [22].

Genetic testing can be helpful given the approximately 15% of FTD cases caused by a recognized genetic mutation. The *C9orf72* mutation can be especially problematic due to its phenotypic heterogeneity, including what can be a very slow progression, very subtle brain imaging changes, and occasional psychotic symptoms. Given that a significant percentage of apparent sporadic bvFTD carry *C9orf72* or *GRN* mutations, The authors state that genetic testing should become standard in all bvFTD cases, and that *C9orf72* testing is increasingly justified in all patients with late-onset behavioral changes suggestive of FTD or with a family history of early-onset dementia/ALS.

Discussion:

The consensus recommendations developed by the Neuropsychiatric International Consortium for Frontotemporal Dementia (NIC-FTD) are an important first step forward in discriminating between bvFTD and primary psychiatric disorders. This is a clinically challenging diagnostic determination, the conclusions of which are significant and impactful for patients, their families, and clinicians and systems serving them. These consensus recommendations therefore will be useful to a wide array of clinicians, including behavioral neuropsychologists, general psychiatrists, neurologists, and other clinicians as well as the programs, institutions, and healthcare environments in which they practice. The authors highlight several possibly underutilized approaches to distinguishing bvFTD from primary psychiatric disorders, including use of social cognitive testing (particularly facial recognition tasks), consideration of serum or CSF NfL, standardized MRI review protocols and PET scanning, and lowered thresholds for genetic testing, particularly for *C9orf72*.

While these consensus recommendations are helpful, they are the first of their kind and therefore must be regarded only as a starting point for evidence-based evaluation and management in this context. Much of what is recommended is necessarily based on relatively weak evidence. The authors have suggested several ways in which the field can be moved forward, including further use of biomarkers and standardized scales.

Many members of the NIC-FTD have prior experience in writing guidelines, though further membership variety, including guidelines specialists, methodologists, and patients and caregivers, may offer additional perspectives on the continued evolution of these consensus recommendations and/or subsequent formal clinical practice parameters or guidelines. In future versions, such recommendations, practice parameters, and/or guidelines may benefit from broader stakeholder involvement [23]. Future research should include further scale development, new physical examination techniques and neuropsychological tests, new methods of neuroimaging analysis, further development of CSF and serum biomarkers, and new approaches to genetic testing.

Specific questions regarding dissemination and implementation questions and challenges also will require consideration in relation to the current and future versions of these consensus recommendations. The NIC-FTD must address at least the following general

areas of dissemination and implementation (adapted from the RE-AIM Planning and Evaluation Framework)[24]:

- *Reach:* How do we make sure they reach eligible patients? Will the patients reached be representative of the larger population? What are the challenges?
- *Effectiveness:* Once implemented, will they have the desired effect? How will that effect be measured?
- *Adoption:* How do we get these guidelines adopted by practitioners? Will they be acceptable? What are the challenges?
- *Implementation:* Will clinicians implement them correctly? Will there be adaptations to the guidelines to fit local context? What will facilitate, what will be the challenges?
- *Maintenance:* Will providers continue using these guidelines long term?

While the NIC-FTD is well positioned to begin identifying key priorities and strategies for implementation, true dissemination of these consensus recommendations will require detailed knowledge about the culture and healthcare systems of each country as well as the local environments (e.g., metropolitan area, institution) in which they are to be implemented. Given the international composition of the author group of these consensus recommendations, dissemination and implementation will require the development of local task forces composed of diverse stakeholders to this process (i.e., patients, families, and medical providers on the front lines of dementia and psychiatric care) in order to identify potential barriers to and facilitators of their dissemination and implementation. Prioritization and identification of the most appropriate and effective means of dissemination will also be required, including designing tools for this purpose, hosting educational events, evaluating and discussing the financial implications of their implementation in local healthcare environments, and other methods of clinician support. Methods of evaluation also will be needed in order to evaluate the success of dissemination and implementation efforts. Additionally, translation of the consensus recommendations into multiple languages is necessary and appropriate, and befitting of the work of an international consortium such as the NIC-FTD.

A plan to periodically review and revise these consensus recommendations in relation to advances in this scientific and clinical practice area is needed. This plan will require integration of knowledge gained through task forces or subcommittees described above, as locally gained knowledge may usefully inform revisions to consensus recommendations for dissemination and implementation at the national and international levels. There is no doubt that scientific advances, including the development of neuroimaging, genetic, or other laboratory test-based biomarkers of bvFTD and primary psychiatric disorders, will shape revisions to these consensus recommendations, although further consideration of the availability, costs, and ease-of-use of such biomarkers will be necessary in relation to their incorporation into future versions of such.

The practical implementation of the present consensus recommendations may be limited by available medical resources and expertise in the area of bvFTD. The consortium attempted

to mitigate this by establishing two levels of recommendations: “Minimal Requirements” and “Clinical Recommendation.” For example, access to neuropsychological assessment is substantially limited or lacking in some localities—in this event, *Minimal Requirements* would include at least a bedside cognitive screening assessment by the clinician performing the diagnostic evaluation. Sometimes, however, even *Minimal Requirements* may present insurmountable obstacles, such as accessibility of genetic testing when a positive family history is present, which is not available in some clinical settings and may not be covered by medical insurance providers even when clinically available. In many situations, a diagnosis of bvFTD versus primary psychiatric disorders may need to proceed regardless of resource limitations and access to available resources. Further work to establish resources for those in rural and other underserved areas may be another focus of the NIC-FTD.

Conclusion

We have here reviewed the recent NIC-FTD consensus recommendations for distinguishing bvFTD from PPD. The NIC-FTD stove to ensure applicability in a variety of communities by explicitly offering recommendations based on at least two levels of available resources, allowing individual practitioners to adjust recommendations to local costs, resource implications, and barriers and facilitators to implementation. As always, clinicians must judge for themselves, in partnership with their patients and their caregivers, how to apply these recommendations in any particular case. Future efforts of the NIC-FTD team may be to incorporate views of local stakeholders in order to understand and ultimately overcome barriers to recommendation adoption, to work alongside psychiatrists to better understand how commonly used psychiatric measures may also discriminate between FTD and primary psychiatric disorders, and to explore ways to expand biomarker and genetic testing and interpretation to underserved communities.

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