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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The behavioral variant of frontotemporal dementia (bvFTD) is the second most common cause of dementia for individuals <65 years old, but accurate diagnosis is often delayed for several years. While previous criteria have increased the ability of diagnosticians to distinguish between bvFTD and other neurocognitive disorders such as Alzheimer's disease, distinguishing bvFTD from a primary psychiatric disorder (PPD) has been more challenging. In early 2020, 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 more than 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. In this article, the authors also review those consensus recommendations and highlight use of novel tests and techniques. Additionally, they indicate where further research is needed, including methods to assess the dissemination and implementation of these recommendations. In this way, future efforts by clinicians and researchers alike to improve accurate recognition of bvFTD are encouraged, thereby expanding opportunities for improved guidance and management.

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The 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 PPD, such as bipolar disorder or schizophrenia (2, 3). Conversely, those with a PPD 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 PPDs 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, transactive response DNA binding protein 43 kDa, or fused in sarcoma 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 disease pathology from frontotemporal lobar degeneration, these criteria are less helpful for distinguishing FTD from PPDs (6).

Until recently, however, there was no standardized consensus on tools to guide practitioners' attempts to distinguish PPDs 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 midlife and late life that may indicate 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 patient history, including clinical scales; psychiatric assessment; physical and neurological examination findings; bedside cognitive tests and neuropsychological examination; tests of social cognition; structural and nuclear imaging; CSF and blood biomarkers; and 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. It has been suggested that a positive family history for psychiatric illness may inappropriately bias diagnoses away from bvFTD (2). Diagnosticians should be wary of such a potential pitfall.

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 PPDs. Examples of potentially useful scales for this purpose include the Frontal Behavioral Inventory 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, Stereotypy Rating Inventory, and the recently developed Frontotemporal Dementia versus Primary Psychiatric Disorder Checklist (8–11).

Careful characterization of bvFTD patients has revealed that most do not fulfill formal DSM-5 criteria for any PPD. Collaboration between a psychiatrist and neurologist may be helpful in diagnostically challenging cases. Although a diagnosis of bvFTD may be more likely in the absence of the emotional distress that is often present in many types of PPDs, 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 toward underlying neurodegeneration, though it is not absolute in either sensitivity or specificity. Parkinsonism, for example, is common in FTD but may also be present in those with PPDs 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 toward 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 use in distinguishing bvFTD from PPDs, given their common occurrence in both types of conditions (12–14).

No bedside cognitive screen has yet been able to clearly discriminate bvFTD from PPDs. While the reviewers postulate on the relative usefulness of different tools, most have been shown to only discriminate between different dementia subtypes or focus more specifically on the executive dysfunction characteristic of bvFTD. Executive dysfunction, however, is highly nonspecific for FTD versus PPDs. 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 PPDs (7). The ACE-III may have some utility in this regard but has been evaluated only at later disease stages, where diagnostic discrimination is generally easier (15).

More detailed neuropsychological assessments may be useful in demonstrating executive dysfunction, but this dysfunction is also common in PPDs. Furthermore, executive dysfunction is not necessarily prominent in bvFTD. Neuropsychological assessments are best used longitudinally to demonstrate decline, which would be more consistent with a neurodegenerative condition. Although this method is diagnostically useful, 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 their efficacy.

Neuroimaging is already an essential component of bvFTD diagnosis; the presence of frontal or anterior temporal atrophy or hypometabolism increases certainty from possible to probable in current criteria (1). However, MRIs may not be obviously abnormal in early stages or in certain variants of bvFTD, such as the *C9orf72* phenotype (17). New analytic techniques may increase sensitivity in the future, but normal brain imaging does not currently absolutely exclude FTLD pathology. Conversely, some PPDs 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 nonspecific patterns of hypometabolism does not necessarily rule out a PPD (20).

CSF and serum biomarkers have less demonstrated utility at present, though markers such as neurofilament light chain may soon point toward 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 disease pathology, a slightly elevated total tau value may also suggest the presence of frontotemporal lobar degeneration when compared with 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 cases 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 NIC-FTD are an important first step in discriminating between bvFTD and PPDs. 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 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 health care environments in which they practice. The authors highlight several possibly underutilized approaches to distinguishing bvFTD from PPDs, including use of social cognitive testing (particularly facial recognition tasks), consideration of serum or CSF neurofilament light, standardized MRI review protocols and PET scanning, and lowered thresholds for genetic testing, particularly for *C9orf72*.

Although 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 move forward, including further use of biomarkers and standardized scales.

Many members of the NIC-FTD have prior experience in writing guidelines. However, greater membership variety, including guidelines specialists, methodologists, and patients and caregivers, may offer additional perspectives on the evolution of these consensus recommendations and subsequent formal clinical practice parameters or guidelines. Future versions of such recommendations, practice parameters, and 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 will also require consideration of 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 [Reach, Effectiveness, Adoption, Implementation, Maintenance] 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 health care 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 health care 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, appropriate, and befitting 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 PPDs 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 PPDs 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.

CONCLUSIONS

We have reviewed the recent NIC-FTD consensus recommendations for distinguishing bvFTD from PPD. The NIC-FTD strove 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 incorporate views of local stakeholders in order to understand and ultimately overcome barriers to recommendation adoption, work alongside psychiatrists to better understand how commonly used psychiatric measures may also discriminate between FTD and PPDs, and explore ways to expand biomarker and genetic testing and interpretation to underserved communities.

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