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INVITED COMMENTARY

Psychiatric Conditions That Can Mimic Early Behavioral Variant Frontotemporal Dementia: The Importance of the New Diagnostic Criteria

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bvFTD is a neurodegenerative brain disorder associated with frontal, insular, and temporal lobar atrophy, characterized during its earliest stages by pervasive changes in personality and behavior, typically reported by the patient's caregivers. Behavioral symptoms include loss of empathy, disinhibition, compulsive behavior, and a shift towards impulsive and socially inappropriate behavior, most of which generally precede the onset of cognitive deficits. Whilst patients with bvFTD usually exhibit deficits on executive functions tests, other cognitive functions, such as visuospatial abilities and praxis, remain relatively well preserved early in the disease (although a subset of patients do present with significant episodic memory disturbance). In the absence of a biological marker, clinical diagnosis of bvFTD depends on the detection of these core neuropsychiatric features, making it difficult for practicing physicians to diagnose early bvFTD. Clinical diagnosis of early bvFTD can, indeed, prove very challenging as a result of several factors. First, early bvFTD patients may exhibit behavioral symptoms, whilst focal atrophy may not be evident on structural brain imaging [1–3]. Additionally, radiologists sometimes report an "unremarkable atrophy pattern," even in the presence of frontotemporal atrophy, which may lead to neglect of behavioral symptoms [4]. Second, changes in social cognition may be overlooked for a long time before they become severe enough to concern the caregivers. Difficulties in social cognition seen in bvFTD are best interpreted as deficits in incorporating contextual information, something that is ubiquitous in social behavior in everyday life but rarely quantified in office-based examinations [5]. Third, patients with early bvFTD may perform entirely within normal limits or be only minimally impaired on standard neuropsychological tests, further delaying early diagnosis. Although bvFTD presents dysexecutive deficits even during the early stages, such dysexecution may go undetected in conventional tests of executive functions as they lack real-life or so-called "ecological" validity. In classic neuropsychological tests conducted in traditional testing environments, the examiner acts as the patient's own executive system [6, 7] .We recently demonstrated that more "ecological" tasks designed to mimic real-life scenarios could detect subtle deficits during the early stages [7, 8]. Nevertheless, the inclusion of such tests is not yet common in clinical practice. Finally, because the wide array of behavioral changes shown by early bvFTD patients overlaps with those found in several psychiatric disorders, subtle neuropsychiatric symptoms in bvFTD may be thought to result from another primary psychiatric condition or may simply be overlooked.

Recent reports have identified a subgroup of individuals that meet clinical bvFTD criteria, but which follow a benign course [9, 10]. These individuals have been referred to as *non-progressors* or *phenocopy* cases. Such patients present with identical clinical features as those with a working

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diagnosis of bvFTD, but have normal brain imaging, better performance on cognitive measures, and relative preservation of activities of daily living. Although the etiology of the non-progressors remains unknown, it has been suggested that these patients may not have an underlying neurodegenerative process. In our experience, most of these phenocopy cases tend to be atypical presentations of psychiatric disorders affecting older adults, including, but not limited to: late onset bipolar disorder, late-onset atypical psychosis, pre-existing personality disorder, atypical depression, age-related personality change, chronic attention-deficit hyperactivity disorder (ADHD), and alcohol abuse [11]. When considering a diagnosis of bvFTD—an incurable disease—it is critical for trained psychiatrists to exclude psychiatric conditions, such as late-life mood disorders, especially in patients without clear frontal atrophy on structural neuroimaging. For example, it has been reported that 10 % of all patients with bipolar disorder develop their illness after the age of 50 years, with bipolar disorder accounting for 5–19 % of mood disorder presentations in older adults [12, 13]. The prevalence of bipolar disorders in late life seems to be greater than previously estimated owing to the existence of atypical presentations, (i.e., the "soft bipolar spectrum"). Similarly, about 14 % of patients with schizophrenia had an age of onset after the fifth decade of life [14–16]. The challenge is, nonetheless, not limited to affective disorders. For instance, ADHD is a lifespan disorder sometimes overlooked or misdiagnosed in early childhood. In some individuals, ADHD goes undetected until they get older and begin to complain of behavioral and cognitive deficits triggered by the increase in age-related executive deficits. This condition, however, is neglected in the differential diagnosis in memory clinics [17]. All in all, the late onset of these and other psychiatric disorders in late life may arise from by a mild, asymptomatic condition in early life that is exacerbated by the aging process, which involves complex interactions between personal and psychosocial stressors.

The key question thus becomes: Where do we draw the line between late onset psychiatric disorders and early bvFTD? Several elements speak in favor of organic, degenerative, frontal etiology: (i) a lack of a family history of mood disorders in the case of late onset mood disorders; (ii) progressive frontotemporal brain atrophy; and (iii) progressive cognitive and functional decline. Further studies are, however, needed to characterize conditions in older individuals that can mimic bvFTD. In this sense, different diagnostic criteria for FTD have been used in the last few decades [18–20]. The accurate diagnosis of bvFTD is increasingly important as a result of potential new disease-modifying therapies [21]. Studies have consistently demonstrated that existing bvFTD criteria are relatively insensitive in the early stages of the disease, which is especially problematic as this is the stage during which disease-modifying treatments can be most effectively implemented [22–24]. An international consortium recently developed revised guidelines for the diagnosis of bvFTD with three levels of diagnostic certainty: possible, probable, and definite [3]. *Possible bvFTD* requires three of six clinically discriminating features (disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviors, hyperorality, dysexecutive neuropsychological profile). *Probable bvFTD* adds functional disability and characteristic neuroimaging [frontal and/or anterior temporal atrophy on computed tomography (CT) or magnetic resonance imaging (MRI), or frontal hypoperfusion or hypometabolism on single photon emission CT (SPECT) or positron emission tomography (PET)]. *bvFTD with Definite frontotemporal lobar degeneration* (*FTLD)* requires histopathological evidence of FTLD or a pathogenic known mutation. The proposed revised guidelines for the diagnosis of bvFTD show better diagnostic accuracy compared with previously established criteria in a bvFTD sample with known FTLD pathology. The increased sensitivity of the new criteria may reflect the optimized diagnostic features, less restrictive exclusion features, and a flexible structure that accommodates different initial clinical presentations. These newly revised guidelines have major implications in discriminating this disorder from other dementias, as well as from other psychiatric disorders and non-degenerative conditions, such as the phenocopy syndrome. The new guidelines are also important for the purpose of clinical trials, as only individuals with the neurodegenerative disease (probable or likely definite bvFTD) should be included.

In conclusion, some psychiatric conditions in late adulthood can mimic early bvFTD and formulating an appropriate differential diagnosis can prove difficult. Aside from investigative tools, such as genetics and neuroimaging, a working clinical diagnosis remains possible only through comprehensive neurological, neuropsychological, and psychiatric tests. Early diagnosis relies, therefore, on a thorough clinical interview and caregiver reports, and requires knowledge of neuropsychology, neurology and psychiatry, with a real interdisciplinary approach. A potential early bvFTD patient should, ideally, be reviewed in the context of a multidisciplinary clinical meeting, where cognitive neurologists, neuropsychologists, and a team of psychiatrists discuss the particulars of each patient. For some patients, especially those who meet criteria for possible bvFTD with normal neuroimaging, a comprehensive psychiatric evaluation is suggested. Only patients with the probable or definite bvFTD according to new international consensus criteria should be included in clinical trials.

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