Crossing borders between frontotemporal dementia and psychiatric disorders: an updated overview

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Words count:
Manuscript: 6242
Abstract: 206
References: 85
Tables: 2

ABSTRACT

Frontotemporal dementia (FTD) includes a group of neurocognitive syndromes, clinically characterized by altered behaviors, impairment of language proficiency, and altered executive functioning. FTD is one of the most frequently observed forms of dementia in the elderly population and the most common in presenile age. As for other subtypes of dementia, FTD incidence is constantly on the rise due to the steadily increasing age of the population, and its recognition is now becoming a determinant for clinicians. FTD and psychiatric disorders can overlap in terms of clinical presentations by sharing a common genetic predisposition and neuropathological mechanism in some cases. Nonetheless, this association is often unclear and underestimated.

Since its first reports, research into FTD has constantly grown, with the identification of recent findings related to its neuropathology, genetic, clinical, and therapeutic issues. Literature is thriving on this topic, with numerous research articles published in recent years. In the present review, we aimed to provide an updated description of the clinical manifestations that link and potentially confound the diagnosis of FTD and psychiatric disorders in order to improve their differential diagnosis and early detection. In particular, we systematically reviewed the literature, considering articles specifically focused on the behavioral variant FTD, published after 2015 on the Pubmed database.

Keywords: Psychiatric disorders, Frontotemporal lobe dementia, Frontotemporal lobar degeneration, Behavioral Symptoms, Differential Diagnosis, Genetics, Neuroimaging, Bipolar Disorder, Schizophrenia.

Introduction

Frontotemporal dementia (FTD) identifies a group of neurodegenerative disorders characterized by a gradual and progressive alteration in behavior or language secondary to atrophy and neuronal loss in the frontal and temporal lobes of the brain [1,2]. Given the numerous functions attributed to these brain regions (e.g., sensorimotor integration and motor control, language performance, emotional regulation, personality, and social behavior), diverse and severely disabling clinical syndromes might result from FTD. Two major clinical subtypes of FTD can be depicted according to their clinical presentation: behavioral variant FTD (bvFTD), which presents as a progressive deterioration and change in social behavior and conduct, and primary progressive aphasia (PPA) otherwise characterized by the slow deterioration of language function and/or semantic memory [3–5].

The presence of psychiatric symptoms could be considered the rule rather than the exception in all types of dementia [6]. PPA might also be associated with psychiatric manifestations. Nevertheless, language alterations most often occur before the onset of psychiatric symptoms, which should alert clinicians to the presence of a neurological disease [7]. This is not the case in bvFTD which most often presents with isolated, less characterized and diverse psychopathologies, making the differential diagnosis a challenge for the clinician [8]. More specifically, bvFTD presents progressive alterations in social behaviour, executive functioning and personality that could easily be misunderstood for primary psychiatric disorders including major depression, bipolar disorder (BD), and schizophrenia [9]. Symptoms such as apathy, disinhibition, and stereotyped/compulsive behavior, changes in eating behaviors, loss of empathy, blunting of affect, hoarding and gambling, are frequently seen in both groups of disorders [10–12]. Moreover, epidemiologic investigation shows that patients with FTD may have experienced psychiatric disorders before the onset of dementia and that patients with psychotic disorders may develop dementia more often than

expected in the non-affected population [6,7,13,14]. Additionally, in recent years, several genetic causes of FTD that predispose to heterogeneous and atypical presentations - including pure psychiatric symptoms - were identified [7]. On one hand, these causes underlie the possible common pathological mechanisms between FTD and psychotic disorders, and, on the other hand, make the correct differential diagnosis a complex and articulated process [7,8]. Furthermore, due to the increasing aging population, neurocognitive disorders are becoming more and more prevalent [15]. Therefore, the need for physicians with expertise in understanding and correctly differentiating these disorders has increased at the same rate.

Methods

In a previous report by our group, we focused on psychiatric symptoms in FTD [7]. In the last five years, however, research in this field has been constantly active with numerous studies published in recent years that had not been included in our previous investigation. Therefore, the aim of the present review was to consider recent publications in order to update readers on the topic. Due to the aim of this review and the different clinical presentations of FTD subtypes, we primarily focused on bvFTD.

For the purpose of the present study, a literature search was performed on Pubmed which considered articles written in English and published from 2015 up until November 2019. To begin with, “frontotemporal dementia” was used as a keyword. Secondly, the following keywords were used in order to refine the results: “frontotemporal dementia” and “psychiatric symptoms”. Lastly, reference lists of selected articles were screened for additional research. Authors considered all of the articles that specifically reported any association, overlap, or difference (in term of epidemiology, neurobiology, clinical presentation, and therapeutic approach) between bvFTD and

psychiatric disorders. Articles that generally described FTD without a specific focus on psychiatric symptoms were not included in the present review.

Results

Epidemiology: FTD and psychiatric symptoms

In the United States, the estimated FTD incidence has been reported at about 3 - 4 per 100,000 people per year, with a prevalence rate of about 15 - 22 per 100.000 in the age between 45 and 65 years, making FTD the second most frequent cause of dementia after Alzheimer's disease (AD) and even more frequent when early-onset dementia is considered [9,16]. A recent Italian study reported FTD incidence to be about 3 per 100.000 people per year [17], while the prevalence in patients aged between 45 and 65 years reached 22 per 100,000 [18]. Considering a neuropathological diagnosis, FTD was found to account 5 to 10 percent of all dementia cases [11,19].

FTD typically manifests in an earlier age compared to other types of dementia. Recent studies have demonstrated that only 10% to 30% of patients show the first symptoms before age 45 and after age 65 respectively, while almost 60% of patients have their onset between age 45 and 65 [16,18]. Although some studies have shown a higher incidence of FTD in male patients, no consistent differences in gender disparity or distribution have been reported [16,20].

With respect to FTD subtypes, bvFTD is the most common clinical form of FTD, representing almost 60% of all cases, especially in samples with early-onset dementia, with a prevalence of 13 people per 100.000 [8,21]. According to a geographical perspective, the bvFTD variant is the most common FTD variant in the United States and Europe (50-70%), while Primary Progressive Aphasia - in its semantic variant - is the most common subtype in Asia [18,19].

Recent studies assessed the prevalence of psychiatric symptoms in bvFTD patients. Psychosis is one of the most frequent and studied psychiatric manifestations seen in FTD patients. According to

a recent review, the prevalence of psychosis in FTD patients characterized as high as 50% of cases [22]. Gossink and colleagues found that more than 95% of patients with probable and definite bvFTD presented at least one psychotic symptom, with negative symptoms such as emotional withdrawal, blunted affect and formal thought disorders being the most frequently represented. Positive symptoms like delusions and hallucinations were only found in the 22% of the sample [23]. In a previous study, psychiatric symptoms in bvFTD patients were even more frequent, with apathy (85%), irritability (65%), disinhibition (60%) and agitation/aggression (55%) being the most represented [24]. BvFTD is highly associated with socially inappropriate behaviors such us disinhibition, irritability, mood elation, impaired social judgment and other behaviors that can mimic mania [9,11]. It is not unusual to observe compulsive behaviors and hyperorality in bvFTD patients. Compulsions, in particular, might even be the initial manifestation of the disease, which can often mimic Obsessive Compulsive Disorder (OCD) [11]. Yet, although these symptoms are common, no recent study has investigated their prevalence in bvFTD patients.

Interestingly, antisocial behavior, impulse control disorder, and cognitive and personality impairment are symptoms that may bring bvFTD patients to legal consequences. In this respect, a recent investigation reported that 14% of patients with bvFTD were initially admitted into psychiatric care due to criminal behaviors [25], highlighting the importance of considering bvFTD in the differential diagnosis even in forensic patients presenting with progressive worsening of cognitive function as well as in patients with new-onset criminal behavior [26].

A previous diagnosis of psychiatric disorders might be present in patients who subsequently develop bvFTD. In this respect, Gossink and colleagues reported a rate of 8.7% of past psychiatric disorders, with unipolar mood disorders being the most prevalent in patients with FTD [27].

Diagnostic criteria and related issues

Diagnostic criteria of bvFTD are based on the consensus criteria published in 2011 by the International behavioral Variant FTD Criteria Consortium (FTDC) [28]. These criteria stratify bvFTD diagnosis hierarchically into three categories: *possible*, *probable* and *definite*. According to these criteria, *possible* bvFTD is diagnosed based exclusively on observation or history (three out of six clinically discriminating features) that prove a progressive deterioration of behavior or cognition or both, *probable* is associated with imaging results consistent with bvFTD (i.e., frontal or anterior temporal atrophy on MRI or hypometabolism on PET), and *definite* bvFTD is supported by neuropathological data (histopathologic evidence of FTD hallmarks) or the presence of a known pathogenic mutation [28].

The fifth edition of the DSM-5 also includes diagnostic criteria for bvFTD within a new classification system for cognitive disorders [29]. Briefly, DSM-5 collects 13 etiological subtypes of acquired primary cognitive disorders, referred to as Neurocognitive Disorders (NCDs) in the same group, further subdivided into Mild or Major NCD. All patients with NCD must exhibit cognitive impairment as a core feature of their respective syndrome. Mild and Major Frontotemporal NCD is included in this chapter: however, only *possible* and *probable* diagnoses are specified. Table 1 (adapted from Lanata and Miller [10]) compares both the FTDC and DSM-5 bvFTD criteria.

Some Authors underlined a possible bias of the new DSM-5 diagnostic criteria that may inadvertently discourage recognition of bvFTD in mental health settings [10]. Specifically, DSM-5 classification relies exclusively on clinical phenotypic profiles rather than on neuroimaging and genetic tests to ascertain the correct diagnosis, which might be difficult considering the important phenotypic overlap between patients with early bvFTD and those with primary psychiatric disorders. Additionally, cognitive impairment is a core feature of bvFTD even though it may be missed, as marked cognitive changes are not necessarily present in the earliest stages of the disease

[10]. Lastly, the DSM-5 does not include a *definite* bvFTD diagnostic category even in case of FTLD-causative genetic mutation, therefore marking it as *probable* bvFTD. In practice, this factor may lead psychiatrists and other physicians to conclude that a bvFTD cannot be diagnosed definitively antemortem with, consequently, no real reason to pursue the correct diagnosis and workup, when, in fact, *definite* bvFTD might be diagnosed with genetic testing [10]. In the proposed classification of the 11TH revision of the International Classification of Diseases [30], FTD defines a group of primary neurodegenerative disorders primarily affecting the frontal and temporal lobes which can be further specified in accordance to the presence of behavioural or psychological disturbances (e.g. psychotic, mood, anxiety symptoms).

Clinical characteristics orienting differential diagnosis

A careful collection of patient's history and a thorough clinical evaluation are the main instruments to make a bvFTD diagnosis [14,31]. Nonetheless, a correct diagnosis is not always easy to obtain because of different aspects that go beyond the simple occurrence of psychiatric symptoms in bvFTD. In fact, patients with psychiatric disorders develop dementia more often than is expected in other populations and subjects with FTD may have experienced previous psychiatric disorders before the onset of FTD [7,27]. Moreover, symptoms can be subtle and slightly defined in the early stages, showing features that are traditionally considered psychiatric manifestations. Patients with bvFTD are often first evaluated in general psychiatric settings, and about 50% of them are initially diagnosed with a primary psychiatric illness [32].

Previously, we reported a diagnostic algorithm that could help clinicians to make a correct differential diagnosis [7]. The most relevant clinical characteristics that support the diagnosis of a psychiatric disorder are an early acute/subacute onset, a positive family history of mood disorders, a history of multiple mood episodes, the presence of comorbidity (anxiety and substance use

disorders), suicidal ideation and previous suicide attempts, inter-episodic complete or partial recovery and cognitive impairment mostly limited to affective episodes. On the other hand, a later/ insidious onset, a positive family history for dementia, a progressive and continuous course, the presence of enduring and progressive cognitive impairment, genetics and neuroimaging evidence, and a poor response to psychiatric treatments support the diagnosis of bvFTD [7].

Several recent studies have continued to analyse this sample of patients in order to understand if specific symptoms selectively characterize bvFTD or psychiatric disorders.

In a recent prospective study, Gossink and colleagues focused on psychotic symptoms in patients with bvFTD compared to patients with different primarily psychiatric disorders, assessed by the Positive and Negative Symptom Scale [27]. Of note, the majority of patients suffered from at least one psychotic symptom (95.5%). In particular, compared to psychiatric patients, bvFTD subjects exhibited stereotypical thinking and difficulties in abstract thinking more frequently, with no difference in respect to positive symptoms [14]. Despite FTD being frequently misdiagnosed as schizophrenia (SCZ), it rarely manifests with delusions and hallucinations, as reported in previous studies [33–35]. Therefore, this result could help in the differential diagnosis. On the other hand, in the same study, patients with psychiatric disorders revealed a higher rate of symptoms belonging to the anxiety spectrum, measured by the PANSS scale (presence of anxiety, guilt feelings, and tension) [27].

In clinical practice, the presence of negative symptoms - in particular alterations in the cognitive functions - are maybe the most difficult obstacle in making a correct diagnosis.

Using a research battery designed to test 16 different cognitive domains, Hui-Minn and colleagues compared bvFTD patients with inpatients with severe chronic SCZ and community-dwelling outpatients with less severe chronic SCZ. Similarly, severe cognitive deficits were found in patients who had poorly functioning chronic SZC and those with bvFTD, higher than in patients with a

milder form of SCZ [36]. While the overall profiles were largely similar, the SCZ group scored worse in confrontation naming and non-verbal reasoning, whereas the bvFTD group was more impaired in letter fluency and immediate memory [36].

General and frontal cognitive functioning, social cognition, and stereotyped behavior were examined in bvFTD compared with primary psychiatric disorders in a two-year follow-up investigation [37]. As a result, frontal behavioral symptoms (e.g., disinhibition, apathy) worsened over time in bvFTD, whereas they improved in psychiatric disorders. Moreover, general and frontal cognitive decline was observed in bvFTD but not in psychiatric disorders, with no differences in stereotypy and social cognition [37]. Overall, the authors proposed that tracking frontal behavioral symptoms and cognition over time might help in correctly differentiating bvFTD from psychiatric disorders.

Another recent study, controversially, reported that cognitive deficits in bvFTD were not more severe compared to those of patients with primary psychiatric disorders with active symptoms (including patients with BD, major depressive disorder, and SCZ) [38]. In particular, a better performance on executive functions and verbal memory emerged in bvFTD patients and, in contrast, bvFTD was associated with worse performance on verbal fluency tests only compared to BD [38]. Clinically, these results indicate that cognitive impairment measured with neuropsychological tests might sometimes help, in ruling out primary psychiatric diagnoses, and that further studies are needed to clarify the role of cognitive deficits.

Catatonia, a clinical presentation classically associated with SCZ, is nowadays considered a specifier applicable to different psychiatric and neurological disorders (DSM-5) and could be described as a manifestation in FTD patients. Some symptoms such as stereotypy, echophenomena, mutism, and perseveration arise both in bvFTD and in catatonia [39–42]. Moreover, some case series reported catatonia as the first clinical presentation in FTD patients [43,44]. In one interesting

case report, authors reported catatonia in psychiatric disorders as being more frequently characterized by a fluctuating trend and usually responding to Lorazepam. In contrast, when catatonia was present in bvFTD, progressive and irreversible deterioration were more common [41]. Overall, in order to differentiate bvFTD from SCZ, the longitudinal course of the disease must be studied. While SCZ tends to manifest in adolescence, the onset of bvFTD before the age of 35 is usually uncommon. Moreover, neurodegeneration in bvFTD is progressive, while psychotic disorders are characterized by the repetition of exacerbations and asymptomatic/more stable phases [11].

Another recent prospective investigation, aimed at exploring characteristics more frequently associated with bvFTD or psychiatric disorders, included patients with a diagnosis of late-onset frontal lobe syndrome. Results showed that a positive history of psychiatric illness, male gender, depressive symptoms, and absence of stereotypy were more frequently associated with psychiatric diagnoses. However, patients with bvFTD showed a higher rate of verbal apraxia, aphasia, impulsivity without irritability, and uncommon calmness and apathy [14]. Once again, in daily clinical practice, specific profiling of clinical symptoms may help in differentiating bvFTD patients from psychiatric patients, and may provide guidance in patient management.

A recent review specifically focused on shared clinical and molecular mechanisms between BD and FTD [45]. According to this investigation, these two subgroups presented similar and diverse characteristics. In particular, BD patients were found to have an earlier age at onset with a course of illness typically influenced by affective phases, while individuals with FTD tend to show a fast progression of the disease. Moreover, inflammation and neurotrophic factors were investigated, with specific pathophysiological pathways involved in these disorders. The authors proposed a hypothetical model of shared mechanisms between bvFTD and BD that includes specific Mendelian mutations (e.g. GRN, c9orf72) with genetic predisposition (e.g. brain-derived neurotrophic factor-

BDNF gene) and environmental factors (e.g. aging, unhealthy habits) with an effect on cellular homeostasis (e.g. increased cell deaths, decreased synthesis of synaptic proteins) and an influence over behavioural and cognitive symptoms [45].

Even though the reported studies seem to support the idea that a differential diagnosis is a real issue for clinicians, other authors underscore an opposing trend contending that the presence of formal psychiatric disorders in bvFTD is not overrepresented [27]. In a recent 2-year longitudinal study, following a correct application of DSM-IV and ICD-10 criteria, the overall frequency of psychiatric disorders in *probable* bvFTD patients (21.7%) did not differ from patients with other neurodegenerative diseases or *possible* bvFTD. An accurate application of diagnostic criteria for psychiatric disorders was proposed by the authors as a successful method for making a correct diagnosis reducing, in this way, the rate of psychiatric misdiagnosis in bvFTD [27].

Possible new clinical diagnostic instruments

In order to help practitioners make the correct differential diagnosis, new possible instruments have been proposed alongside with historical and clinical evaluation.

Ducharme and colleague recently proposed a new clinical tool to help clinicians differentiate bvFTD from other psychiatric disorders. Through a literature review, the authors developed a checklist of clinical features differentiating bvFTD from primary psychiatric disorders (PPD). The checklist contained 17 items and was then piloted, prospectively and retrospectively, in two cohorts of patients presenting with behavioral changes suggestive of bvFTD whose diagnosis was confirmed after the follow-up. As a result, a score of ≥11 was found to be strongly indicative of bvFTD, while a score of ≤ 8 was strongly indicative of a PPD. Patients with scores of 9 or 10 were considered in the “indeterminate zone” because these scores were seen across all diagnostic groups,

including other neurocognitive disorders. This study suggested that the short checklist might be promising as a simple and useful clinical tool to improve diagnostic accuracy [46].

As previously reported, cognitive functions are broadly affected in both bvFTD and psychiatric disorders and it is not always simple to differentiate which specific domain characterizes one or the other disease. Recently, the *Ekman 60 Faces,* a cognitive test that specifically assesses social cognition, was proposed in this group of patients in a longitudinal multicenter study [23]. In the result, bvFTD patients obtained lower scores in the *Ekman 60 Faces* test compared to those with any other neurodegenerative diseases and psychiatric disorders included in the study. Other cognitive domains were not discriminative. A similar result was replicated by Chiu and colleagues who used a similar test (a novel facial emotion intensity rating task) helpful in differentiating patients with bvFTD and major depression, confirming different emotion processing paradigms between the two groups of patients [47]. On the other hand, Reus and colleagues found no difference in social cognition between bvFTD and primary psychiatric patients in social cognitive functioning [37]. These studies underlie the need for more original studies and literature meta-analysis to clarify the utility of specific neuropsychological examinations in the diagnostic procedure of bvFTD.

Other psychometric scales have shown some utility in differentiating patients with bvFTD and psychiatric disorders. In recent studies, a low Stereotypy Rating Inventory (SRI) score [48,49] and a high Montgomery–Asberg Depression Scale (MADRS) score were predictive for a psychiatric disorder compared to bvFTD [49]. Moreover, less stereotypy (based on a low score on the SRI), and more depressive symptoms (based on high scores on the MADRS) associated with male gender were found to have a good predictive ability in discriminating psychiatric disorders versus probable/ definite bvFTD in a cohort of patients with late-onset behavior changes [50]. In another investigation, the PANSS total score of the negative subscale was significantly higher in patients

with bvFTD than in patients with a psychiatric disorder, while the PANSS total score of positive subscale was not different [27].

Interestingly, cerebrospinal fluid (CSF) examination was proposed as a potential diagnostic tool to help in the differential diagnosis [51]. CSF has a great diagnostic value in the diagnosis of dementia, especially in Alzheimer's disorder [52], and it was proposed to use this procedure to differentiate patients with bvFTD and primary psychiatric disorders. As a result, the CSF levels of three biomarkers involved in the pathophysiology of FTD - NfL (neurofilament light chain), p-tau/tau ratio (phosphorylated-tau to total-tau ratio), and YKL40 (chitinase-3 like-1, cartilage glycoprotein-39) - were found to be the best discriminators between the two groups of disorders, with a sensitivity of 91% and specificity of 83% considering the combination of these three biomarkers. In fact, higher levels of CSF NfL and YKL40 and reduced p-tau/tau ratio have shown good accuracy in distinguishing bvFTD from psychiatric disorders and will potentially become in the the future suitable biomarkers [51]. Following the neuropathological perspective of the above-mentioned study, another recent investigation measured the levels of NfL in a blood sample. As a result, serum NfL levels were significantly elevated in bvFTD patients compared to the controls (depressed, schizophrenic and bipolar patients [53]), proposing NfL serum as a possible biomarker in differentiating bvFTD from psychiatric disorders and as a method to rule out neurodegeneration in the course of psychiatric disorders.

New neuroimaging insights

Neuroimaging plays an important role in the diagnosis of bvFTD. A *probable* diagnosis of bvFTD can be made considering specific brain abnormalities consistently related with bvFTD, specifically in the fronto-insular and temporal cortices, dorsomedial prefrontal cortex, striatum, and thalamus [54,55]. Moreover, neuroimaging studies have given a considerable contribution to the

understanding of the neuropathology of FTD and even in the differential diagnosis between psychiatric disorders.

In this respect, Baez and colleagues recently compared subjects with late-onset BD and bvFTD in terms of neuropsychological and neuroanatomical assessment using voxel-based morphometry. Compared to BD, bvFTD patients exhibited a significant decrease in gray matter (GM) volume in frontal, temporal and parietal regions. From a neuropsychological perspective, atrophy in specific brain regions were associated with specific cognitive impairments in bvFTD compared with BD patients. In the former group, atrophy of frontal, temporal and insular cortices was related to executive functioning deficits. Moreover, atrophy of the amygdala, hippocampus, parahippocampal gyrus, putamen, insula, precuneus, right temporo-parietal junction and superior temporal pole was associated with the theory of mind impairments. No significant associations between atrophy and executive functioning performance were observed in BD patients [56]. These results seem to provide additional evidence to discriminate bvFTD and late-life BD as distinct clinical entities and support the use of neuropsychological and structural imaging assessments for the differential diagnosis.

Interestingly, an MRI based investigation found that right anterior temporal atrophy and sparing of the left frontal lobe were specifically associated with bvFTD patients with psychotic-like speech (i.e pressure of speech, tangentiality, derailment, clanging/rhyming, and punning) in the absence of other psychotic symptoms [33].

Additionally, positron emission tomography scans have shown a role in differentiating bvFTD from other forms of dementia [57,58]. Late-onset BD and bvFTD patients were also assessed and compared with MRI and PET, reporting structural and functional different abnormalities [59]. More specifically, BD patients showed grey matter reduction in the ventrolateral prefrontal cortex and greater grey matter volumes in the caudate nucleus. On the other hand, bvFTD patients reported

grey matter reductions in the dorsolateral prefrontal cortex and volumetric and metabolic reductions within the orbitofrontal cortex, volumetric shrinkage in regions within the temporo-parietal network as well as greater metabolic impairments within the temporal cortex, more extensive volumetric and metabolic abnormalities within the limbic lobe, and lastly, a greater metabolism in caudate nucleus. Finally, while the BD group showed greater grey matter volumes in the caudate nucleus, bvFTD subjects reported a lower metabolism [59].

Additionally, a recent investigation identified how specific neuroanatomical abnormalities (analyzed through voxel-based morphometry) correlated with psychiatric symptoms in patients carrying a gene mutation suggestive of bvFTD [60]. As a result, the main forms of genetic FTD showed distinct neuroanatomical correlations with neuropsychiatric symptoms (i.e. strong association of psychotic symptoms with GM atrophy in the anterior insula for the group with GRN mutation; presence of mood disorders mostly associated with GM atrophy in frontal-insular cortex for the group with GRN mutation; cerebellar atrophy found to only correlate with anxiety in C9orf72 carriers; delusions in C9orf72 expansion carriers prevalently associated with left frontal cortical atrophy). Overall, these findings support the concept of brain structural changes overlapping between FTD and primary psychiatric disorders that may be mediated by the alteration of common genes relevant in structures involved in large-scale networks [60].

More recently, a combination of neuroimaging data and clinical information collected at baseline has been used in machine learning algorithms in order to predict two-year follow-up diagnosis in patients with bvFTD, psychiatric disorders, and other neurological disorders. This technique demonstrated a good accuracy in distinguishing bvFTD from other neurological disorders and psychiatric disorders in particular [48]. Therefore, this machine-learning algorithm might be a future valuable instrument for clinicians to obtain an early and accurate diagnosis [48].

New research in genetics

Genetics play an important role in the neuropathology of bvFTD: up to 50% of patients have a positive family history of dementia [19] and approximately one third of FTD cases has a known genetic cause, supporting the assumption that this disorder might be highly heritable [21]. Moreover, they also have an important role in the diagnosis because, according to FTDC criteria, a genetic test can lead to an ante mortem *definite* bvFTD diagnosis.

Neuropsychiatric symptoms are quite common in FTD related mutation carriers [60], underlining the overlap between FTD and psychiatric disorders in terms of neuropathology. In our previous report, we already listed the most common genetic mutations related to this condition. Briefly, the most prevalent mutations associated with familial FTD are a repeated expansion of an intronic hexanucleotide (GGGGCC) in the chromosome 9 open reading frame 72 (C9orf72) gene (~30%), followed by mutations in the genes for progranulin (GRN~20%) and microtubule-associated protein tau (MAPT, ~10%). Psychiatric symptoms are frequently present in C9orf72 carriers and, to a lesser extent, in GRN carriers [45]. Less frequent mutations include Valosin-containing protein (VCP), charged multivesicular body protein 2B (CHMP2B), ubiquilin 2 (UBQLN2), sequestosome 1 (SQSTM1), TAR DNA binding protein (TARDBP) and fused RNA binding protein (FUS) [7,61,62].

In order to better clarify the etiology of this heterogeneous disorder and its relationship to neuropsychiatric symptoms, recent gene investigations analyzed the association between genetics and clinical course of the illness. The C9orf72 mutation consists of a repeated expansion of a hexanucleotide (GGGGCC) in the first intron of the gene, which shows an autosomal dominant pattern of inheritance. Studies have shown a relatively strict correlation between C9ORF72 expansion and the presence of neuronal inclusions containing TAR DNA binding protein (TDP-43) on neuropathological examination [61]. In terms of clinical presentation, patients with a C9orf72

expansion typically present with bvFTD, a motorneuron disease (MND) or a combination of both [7].

As far as cognitive functioning is concerned, patients often show a decline in visual and verbal episodic memory, apraxia, anomia, dyscalculia, and reduced spontaneous speech. On the other hand, language seems to be impaired less frequently than in patients with GRN or MAPT mutations [61]. Neuropsychiatric symptoms like somatic delusions and, more broadly, psychotic symptoms are more common in C9orf72 carriers than in non-carriers, while the rate of hallucinations does not seem to differ between the two groups [63,64]. In a case series, Shinagawa and colleagues described how C9orf72 carriers with well-defined delusions were likely associated with additional pathologies (i.e. Parkinsonism) and parietal atrophy in neuroimaging, underling a common neurophathology between FTD and delusion [65]. Affective symptoms, anxiety, suicidal behavior, and obsessive-compulsive disorder may be present as well [7,19,66].

Another gene often associated with FTD is progranulin (GRN), whose frameshift and non-sense mutations result in the reduction of circulating levels of progranulin, a glycoprotein involved in lysosomal functions, neurite growth, synaptic transmission and neuroinflammation [62]. Autosomal dominant, with variable penetrance, is the typical pattern of inheritance [7]. FTD patients with progranulin mutations often present as bvFTD or, less frequently, with progressive PPA. Typical clinical presentation features are apathy and social withdrawal, and in a minority of cases, episodic memory impairment. In regards to neuropsychiatric symptoms, delusions, hallucinations and ritualistic behaviors may be present. Of note, an early language impairment is more frequent compared with cases with C9orf72 or MAPT mutations. The frequency of extrapyramidal symptoms stands around 40-60% [61].

Interestingly, a reduction of progranulin was detected not only in bvFTD but in BD as well. In a recent article, Zanardini reported that an imbalanced expression of this neurotrophin in specific

brain regions and in different periods of life might result in either neurodegenerative or psychiatric diseases. Moreover, subjects with progranulin deficit might present with psychiatric symptoms that could represent a preclinical phase preceding FTD [67,68]. Consistently, a recent case report documented a case of late-onset BD that developed into bvFTD over time in a patient carrying a GRN mutation [69]. Ultimately, studies suggest a close relationship between manic behavior and bvFTD, even though the nature of this correlation is still unclear and needs to be explored in further investigation [68].

The MAPT gene encodes the microtubule-associated protein Tau, which is involved in microtubule stabilization and assembly. Research studies have allowed the identification of more than 40 mutations of MAPT, involving different areas of the gene and variably affecting tau function. These mutations interfere with protein function by promoting tau aggregation, hindering microtubule binding and altering isoforms ratio [7]. The pattern of inheritance is autosomal dominant, with high penetrance. From an anatomo-pathological perspective, patients typically present with tau-positive inclusions (FTLD- Tau) [7].

The clinical features of patients with MAPT-associated FTD are heterogeneous with regard to both symptoms and age of onset [7]. An interesting recent case report analyses an Argentinean family with a family history of bvFTD with an autosomal dominant pattern of inheritance, including one sibling diagnosed with Cortico-Basal Syndrome (CBS) and another one with FTD. Researchers found a missense mutation (p.P301L) in exon 10 of the MAPT gene in both affected siblings. Among MAPT mutations, p.P301L is most often associated with the following clinical syndromes: early-onset Parkinsonism, late Parkinsonism associated with FTD, Progressive Supranuclear Palsy (PSP) and, exceptionally, CBS. This report highlights the marked phenotypic heterogeneity not only among unrelated individuals but also within the same family [70]. With respect to psychiatric symptoms, the most common features of MAPT-associated FTD include disinhibition, poor impulse

control, loss of insight, stereotyped repetitive behaviors, obsessions, mental rigidity and lack of social awareness or context, whereas apathy is less common than in PGRN and C9orf72 cases. Mood and anxiety disorders, on the other hand, seem less common in patients with MAPT mutation, except for depressive disorder not otherwise specified, an atypical syndrome characterized by clinically significant depressive symptoms, which fail to meet criteria for major depressive disorder [71]. Other clinical features include episodic memory loss, which might lead to the diagnosis of early onset Alzheimer's disease (AD) and semantic impairment, which often appears later during the course of the disease [61].

Ultimately, Gotovak and colleagues highlighted a new correlation between the APOE e4 allele and aggressive symptoms in FTD [72].

Even though the above-mentioned mutations seem to play a key role in the etiopathogenesis of the disorder, most FTD cases are the result of complex - and yet to be fully understood - interactions between genetic, epigenetic and environmental factors. BvFTD must, therefore, be considered a multifactorial disease. Nevertheless, clinicians should be able to apply current evidence about genetics in clinical practice and hypothesise a genetic etiology when taking patients with FTD into consideration. A family history dating back to three generations should be carefully investigated with a focus on the neuropsychiatric symptoms, and if a familial form of the disorder is suspected, both the patient and the family should be referred to genetic counselling [16]. In this respect, genetic testing should be considered in patients with FTD and a strong family history of autosomal dominant neurological disorders including FTD, AD, Parkinsonism, MND, inclusion body myopathy, or late-onset psychosis with insidiously worsening course [18,73].

Possible new therapeutic approaches and disease prognosis

Alongside the complexity of the clinical presentation and the difficulties encountered in making the correct differential diagnosis, the therapeutic approach is a challenging issue for clinicians.

To date, there are no United State Food and Drug Administration (FDA) approved therapies for FTD, and there are no treatments that can stop or alter the course of disease progression [74]. Thus, medication typically prescribed for other types of dementia and psychiatric syndromes are frequently used as off-label treatments for FTD [75]. This could mainly be due to the paucity of large, double blind, randomized controlled trials with the available knowledge of therapeutic strategies mainly based on small case series [74]. The majority of treatment intervention is aimed at obtaining symptomatic relief (improving behavioral, cognitive, or motor symptoms) by using a variety of agents with mixed results in terms of efficacy [74].

Currently, the treatment for cognitive symptoms is based on acetylcholinesterase inhibitors (e.g. donepezil, galantamine, rivastigmine). No consistent data on improvement is reported in literature, with some investigation reporting that acetylcholinesterase inhibitors may worsen behavioral disturbances in FTD [76]. Memantine, an NMDA-antagonist, has been proposed as an alternative therapy in FTD; however it currently lacks clear therapeutic benefits [77].

Considering the high prevalence of patients with psychiatric symptoms, current FTD pharmacologic strategies have specifically focused on the modulation of behavioral symptoms. These medications include a variety of antidepressant effects that could target both depressive symptoms (such as apathy and abulia) and aggressiveness, irritability, disinhibition, and delusions [61]. Among these drugs, some reports supported the use of selective serotonin reuptake inhibitors (such as citalopram, paroxetine, sertraline), and serotonin modulators (trazodone) [78] and the dopamine-norepinephrine reuptake inhibitor bupropion [79]. Agomelatine, but not melatonin, was associated with a significant reduction of apathy in FTD subjects [80].

While antipsychotics have long been used to control behavioral alterations, evidence for their use in FTD comes mainly from case reports and uncontrolled series [81]. Pharmacological approaches aimed to control behavioral symptoms involve the use of atypical antipsychotics (quetiapine, risperidone, aripiprazole, olanzapine) and of anti-epileptics with mood stabilizing effects such as valproic acid, topiramate and carbamazepine. For these pharmacological compounds, the effects are variable and evidence is mostly limited to case reports as well [76]. Additionally, antipsychotic use is often associated with severe adverse effect profiles. Of note, there is an increased susceptibility to extrapyramidal symptoms after antipsychotic use in patients with FTD [82].

Alongside the pharmacological approach, non-pharmacological interventions are considered along with pharmacological therapies. These interventions include providing caregivers with information, emotional support, strategies for behavioral management, and access to community resources with the aim to support the patient and to reduce the high burden of distress perceived by caregivers [8,24,61]. A multidisciplinary team approach involving physicians (neurologists and psychiatrists), nursing, physical therapy, and other rehabilitative services, as well as social work and caregiver/ family involvement, is often required for the optimal management of patients with psychiatric disorders in dementia [6].

The difficult therapeutic management, alongside the difficulties in the differential diagnosis, have a dramatic impact on the prognosis of this disorder. The survival time of patients affected with FTD is usually 2 to 11 years from symptoms onset [21,83]. According to Lee et al., the prognosis of patients with bvFTD varies according to the extent of atrophy of the frontal lobe visible at the MRI. In fact, in their study, the survival time was shorter in patients with bvFTD who show diffuse frontal lobe atrophy (6.9 years) than in bvFTD patients with focal or circumscribed frontal lobe atrophy (9.4 years) on MRI [84]. Considering that diagnosis is often delayed, the survival time after diagnosis is only 4 years for bvFTD. Moreover, a low prognosis could have been associated to a

high prevalence of suicidal risk in this population, which is particularly high in younger patients with longer illness duration and associated to higher levels of anxiety and depression [85]. Additionally, the diagnosis of FTD as a single or comorbid condition with other psychiatric disorders significantly worsens the general prognosis [6,7]. Other characteristics associated with a worse prognosis include a shorter disease duration at presentation, a greater atrophy in the anterior cingulate cortex, an older age, and a higher burden of behavioral symptoms [83].

Lastly, a known pathogenic frontotemporal dementia mutation was reported as being the strongest predictor of disease progression [83]. However, no prognostic markers are available and predicting the course of the disease for a singular patient remains difficult [18–20].

Conclusions

Table 2 summarizes the most recent findings (post 2015) that may be helpful in differentiating bvFTD from primary psychiatric disorders. In conclusion, FTD comprises different expressions of pathology, which may pose significant challenges to clinicians for differential diagnosis with primary psychiatric disorders, particularly for bvFTD. While imaging and genetic characterization can help to orient clinicians toward the right diagnosis, an accurate clinical investigation with particular attention to family history, age at onset, previous subclinical episodes, type of course and comorbidity patterns, still remains the most useful approach to obtain a correct diagnosis in clinical practice. While a robust body of evidence is now available in the field, many clinicians do not operate in team and delayed/misdiagnosis with unsuccessful treatments represent the most frequent consequences of such an approach. Even though effective treatments for bvFTD are currently lacking, symptomatic interventions may still prove useful for affected patients, while supportive interventions of pharmacological and psychotherapeutic nature may be helpful not only for patients but for their caregivers as well.

ACKNOWLEDGMENTS AND DISCLOSURES

Prof. Dell'Osso has received Grant/Research Support from LivaNova, Inc., Angelini and Lundbeck and Lecture Honoraria from Angelini, FB Health and Lundbeck. Dr. Vismara, Dr. Cirnigliaro, Dr. Piccoli, Dr. Molteni, Dr. Giorgetti, Dr. Fumagalli, Dr. D'addario, and Dr. Cremaschi report no potential conflict of interest.

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TABLES

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FTDC		DSM 5		Differences
Possible bvFTD	Three or more of the following 6 features: ► Early behavioural disinhibition ► Early apathy or inertia ► Early loss of sympathy or empathy ► Early perseverative, stereotyped or compulsive/ ritualistic behaviours ► Hyperorality and dietary changes ► Deficits in executive function with relative sparing of episodic memory and visuospatial skills (as determined by structured neuropsychological testing)	Possible (mild or major) bvFTNCD	Prominent decline in social cognition AND/OR executive function with relative sparing of memory and perceptual-motor (visuospatial) function, AND three or more of the following 5 features: ► Behavioral disinhibition ► Apathy/inertia ► Loss of sympathy/ empathy ► Perseverative, stereotyped or compulsive/ ritualistic behaviour ► Hyperorality and dietary changes	DSM-5 requires cognitive impairment (in social cognition and/or executive function) to be present; FTDC makes it optional FTDC specifies 'early' as occurring within 3 years of presentation
Probable bvFTD	Possible bvFTD AND evidence of BOTH the following: ► Significant functional decline ► Frontal and/or anterior temporal lobe atrophy on MRI or CT, or frontal and/ or temporal hypoperfusion or hypometabolism on PET or SPECT	Probable (mild or major) bvFTNCD	Possible bvFTD AND evidence of EITHER of the following: ► An FTLD pathogenic Mutation ► Disproportionate frontal or temporal lobe involvement on neuroimaging	DSM-5 requires functional decline at the level of syndromic diagnosis of Major NCD, before bvFTD subtype; FTDC does not distinguish bvFTD in mild/major categories DSM-5 places genetic mutations as evidence of probable bvFTD; FTDC places genetic mutations as evidence of definitive bvFTD (see below)
Definite bvFTD	Possible OR probable bvFTD AND evidence of EITHER of the following: ► Histopathological changes consistent with FTLD on biopsy or autopsy ► Presence of known FTLD pathogenic genetic mutation	Not applicable	Not applicable: clinical diagnosis only	DSM-5 does not provide a definite (mild or major) bvFTNCD diagnostic category

Legend: FTLD, frontotemporal lobar degeneration; FTNCD, Frontotemporal Neurocognitive Disorder; PET, positron emission tomography; SPECT, single-photon emission CT.

Table 2: most recent investigations orienting differential diagnosis between bvFTD and primary psychiatric disorders.

Investigation	**BvFTD**	**Primary psychiatric disorders**
History and clinical examination	Later/insidious onset, positive family history for dementia, progressive course, presence progressive cognitive impairment, poor response to psychiatric treatments (Galimberti, 2015).	Early acute/subacute onset, positive family history of mood disorders, history of multiple mood episodes, presence of comorbidity (anxiety and substance use disorders), suicidal ideation and/or previous suicide attempts, inter-episodic complete or partial recovery and cognitive impairment mostly limited to affective episodes (Galimberti, 2015).
Psychometric evaluation (PANSS, MADRS, SRI)	Stereotypical thinking and difficulties in abstract thinking (Dols, 2016). Significantly higher PANSS total score of the negative subscale (Gossink, 2016).	Low SRI and high MADRS score (Dols, 2016b). Higher rate of symptoms belonging to the anxiety spectrum measured by the PANSS scale (Gossink, 2016).
Neuropsychological tests	Impairment in letter fluency and immediate memory (Chan, 2015) and progressive worsening of frontal behavioural symptoms (Reus, 2018).	Impairment in confrontation naming and non-verbal reasoning (Chan, 2015).
CSF biomarkers	High levels of CSF NFL and YKL40; reduced p-tau/tau ratio (Vijverbergs, 2017).	
Serum biomarkers	Elevated NFL levels (Al Shweiki, 2019).	
Magnetic resonance imaging	Volumetric reductions in the dorsolateral prefrontal cortex and within the orbitofrontal cortex and temporo-parietal regions (Baez, 2019). Extensive volumetric abnormalities within the limbic lobe (Delvecchio, 2019).	Grey matter reduction in the ventrolateral prefrontal cortex, greater grey matter volumes in the caudate nucleus (Delvecchio, 2019).

Voxel based morphometry	Decrease in gray matter volume in frontal, temporal and parietal regions (Sellami, 2018).	
Positron-emission tomography	Metabolic impairments within the orbitofrontal and temporal cortex, metabolic abnormalities within the limbic lobe and greater metabolism in caudate nucleus (Delvecchio, 2019).	Lower metabolism in the caudate nucleus (Delvecchio, 2019).
Genetic testing	C92ORF, GRN mutation and MAPT mutation (Galimberti, 2015).	
Neuropathological examination	TDP43 and Tau-positive inclusions (Young, 2018).	

Legend: PANSS: Positive and Negative Syndrome Scale, SRI: Stereotypy Rating Inventory, MADRS: Montgomery-Åsberg Depression Rating Scale, CSF: Cerebro-spinal fluid, NFL: neurofilament light polypeptide.