Bipolar Disorder Among Patients Diagnosed With Frontotemporal Dementia

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Objective: Previous studies have documented manic and hypomanic symptoms in behavioral variant frontotemporal dementia (bvFTD), suggesting a relationship between bipolar disorder and bvFTD.

Methods: The investigators conducted a literature review as well as a review of the psychiatric histories of 137 patients with bvFTD, and patients with a prior diagnosis of bipolar disorder were identified. The clinical characteristics of patients' bipolar disorder diagnosis, family history, features of bvFTD, and results from fluorodeoxyglucose positron emission tomography (FDG-PET), as well as autopsy findings, were evaluated.

Results: Among the 137 patients, 14 (10.2%) had a psychiatric diagnosis of bipolar disorder, eight of whom met criteria for bipolar disorder (type I, N=6; type II, N=2) 6–12 years preceding onset of classic symptoms of progressive bvFTD. Seven of the eight patients with bipolar disorder had a family history of mood disorders, four had bitemporal predominant hypometabolism on FDG-PET, and two had a tauopathy involving temporal lobes on autopsy. Three additional patients with late-onset bipolar I disorder proved to have a nonprogressive disorder mimicking bvFTD. The remaining three patients with bvFTD had prior psychiatric symptoms that did not meet criteria for a diagnosis of bipolar disorder. The literature review and the findings for one patient further suggested a shared genetic mutation in some patients.

Conclusions: Manic or hypomanic episodes years before other symptoms of bvFTD may be a prodrome of this dementia, possibly indicating anterior temporal involvement in bvFTD. Other patients with late-onset bipolar disorder exhibit the nonprogressive frontotemporal dementia phenocopy syndrome. Finally, a few patients with bvFTD have a genetic predisposition for both disorders.

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Behavioral variant frontotemporal dementia (bvFTD) is a progressive neurodegeneration of the frontal and anterior temporal lobes that usually presents in mid-life, with alterations in personality and emotional regulation (1, 2). bvFTD, which is the second most common dementia among patients <65 years old (3), includes progressive decline in executive and other cognitive abilities, as well as behavioral changes (4). The earliest personality and emotional features tend to be apathy or abulia, disinhibition or impulsivity, and loss of sympathy or empathy (2); however, a wide range of behavioral symptoms can occur, including manic-like behavior and symptoms (5, 6). Many, if not most, patients with bvFTD present to psychiatrists who have to distinguish early bvFTD from primary psychiatric disorders (7).

Some patients with bvFTD can appear similar to patients with bipolar disorder on initial presentation (8–10). Patients can manifest with euphoria or emotional outbursts, talkative or pressured speech, racing thoughts, task-oriented behavior, increased energy, and psychomotor activity, as well as irritability, distractibility, and disinhibition (6, 8, 11). Conversely, the manifestations of bipolar disorder include not only manic hypomanic or depressive episodes (12, 13) but also neurocognitive impairments in complex attention, executive functions, and other changes similar to bvFTD (4, 14–16).

This overlap in symptoms of bipolar disorder and bvFTD suggests possible shared origins and mechanisms between these two disorders and raises the question of whether bipolar disorder precedes or leads to bvFTD (17). Indeed, a number of investigators have reported a link between the two disorders (18, 19), yet the exact association is unclear. We hypothesized that beyond shared presenting symptoms, manic or hypomanic episodes can be a prodrome of bvFTD in some patients, and late-onset bipolar disorder can present as a bvFTD mimic or FTD phenocopy in others (20, 21). Accordingly, we reviewed our clinical base of well-diagnosed patients referred for bvFTD who also had a psychiatric diagnosis of bipolar disorder and reviewed the literature on the association between these two disorders.

METHODS

Participants

The participants presented for evaluation at a university clinic specializing in bvFTD. All patients had neurobehavioral changes suggestive of bvFTD and underwent a comprehensive evaluation, laboratory assessment, and MRI. In addition, most had fluorodeoxyglucose positron emission tomography (FDG-PET) of the brain. A total of 137 patients met initial clinical criteria for bvFTD (possible, probable, or definite) for the present review (2). To be included in this study, patients diagnosed with bvFTD had to have a knowledgeable informant and an initial history of progressive deterioration of behavior or cognition from their prior normal baseline level. Changes in behavior or cognition included three of the following symptoms: apathy, disinhibition, loss of empathy, repetitive behaviors, dietary changes, and a predominant dysexecutive cognitive profile (2). Patients met criteria for possible bvFTD unless neuroimaging showed frontal or anterior temporal changes supportive of a diagnosis of probable bvFTD or there was definite bvFTD on neuropathology. Among the 137 patients with bvFTD, we further identified all those who had a prior diagnosis of bipolar disorder made by a psychiatrist. This study was approved by the institutional review board of the University of California Los Angeles.

Procedures

For the subgroup of patients with a prior psychiatric diagnosis of bipolar disorder, we abstracted historical evidence of the previous psychiatric symptoms that led to their bipolar disorder diagnosis, focusing on mania, hypomania, or a history of elevated, expansive, or irritable mood (22). We evaluated criteria for manic or hypomanic episodes that included three of the following symptoms: inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or feeling pressured to continue talking ("press of speech"), flight of ideas or subjective experience that thoughts are racing, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in activities that have a high potential for painful consequences. Additionally, we assayed criteria for depression or depressive episodes and family history suspicious for mood disorders.

RESULTS

Among the 137 patients, 14 (10.2%) had a preceding psychiatric history reported to be indicative of a bipolar spectrum disorder. On review, three of these patients did not meet criteria for bipolar disorder but had a history of other psychiatric symptoms that led to their bipolar disorder diagnosis, including suicidal behavior, paranoia, impulsivity, antisocial behavior, and obsessive-compulsive behavior. The remaining 11 patients comprised two subcategories: the prodromal and phenotype subgroups.

Prodromal Group

Eight patients (males, N=6; females, N=2) had an identifiable past history of mania (bipolar I disorder, N=6) or hypomania (bipolar II disorder, N=2) occurring 6–12 years before an established diagnosis of progressive bvFTD. The mean age at onset of mania or hypomania (48.25 years [SD=13.0]) preceded the mean age at onset of bvFTD (57.25 years [SD=11.9]) by an average of 9 years. For one patient, we could not verify any past psychiatric and family histories because of the patient's immigrant status and loss of family members to war. The other seven patients had a positive family psychiatric history, usually for depression, and one patient had a chromosome 9 open reading frame 72 (C9orf72) mutation. Of the eight patients in the prodromal group, four had prominent bitemporal hypometabolism with or without frontal involvement on FDG-PET, and one other had less prominent temporal lobe hypometabolism. Most of the changes were bilateral at the time of imaging, and no clear laterality difference was discerned. Details of the demographic and clinical characteristics of the prodromal group are presented in Table 1. Patients with autopsies (N=2) exhibited FTD changes with tau positive intranuclear inclusions, involving the frontal and temporal neocortex in one patient and inferior temporal lobes in the other patient.

Phenotype Group

Three additional patients (males, N=2; female, N=1), comprising the phenotype group, did not meet criteria for progressive bvFTD because they did not have frontotemporal changes on FDG-PET and did not manifest clinical worsening of FTD behaviors or neurocognitive measures when followed for 3–7 years. The mean age at onset of manic episodes (58.87 years [SD=3.21]) preceded the mean age at onset of bvFTD (60.0 years [SD=1.0]) by about 1 year.

Additional Observations

Other characteristics of patients with mania or hypomania were obtained. All patients with manic episodes underwent psychiatric hospitalization, and most manic episodes were with psychotic features. All except two patients were taking various antipsychotic medications, and only one patient was taking lithium. Depressive episodes were present in six patients with subsequent progressive bvFTD but not in the three nonprogressive patients, all three of whom had severe, recurrent manic episodes with hospitalization. Only one patient approached being a rapid cycler (patient 8). Another patient was reported by relatives to be cyclothymic during his college years (patient 4). This same patient had his initial and persistent manic episode precipitated by antidepressant medication, but there was no other evidence of substance-abuse-induced mania or drug-induced mania. Otherwise, all manic and hypomanic episodes were of relatively late onset, with the possible exception of those

TABLE 1. Behavioral variant frontotemporal dementia (bvFTD) in patients with bipolar disorder

Patient (gender)	Mania/hypomania	Psychiatric symptoms age at onset (years)	bvFTD criteria	bvFTD age at onset (years)	Family psychiatric history	FDG-PET imaging[a]
1 (female)	No: suicidal, paranoia	25	Yes: probable	34	Yes: depression, suicidal	Right frontal, bitemporal
2 (female)	Yes: mania plus psychosis, depression	37 for depression, 40 for mania	Yes: probable	48	Yes: suicidal	Bifrontal (worse on the left side)
3 (male)	No: suicidal, impulsive	58	Yes: probable	58	Unknown	Bitemporal
4 (male)	Yes: treated depression followed by persistent mania	33 (cyclothymia 20s)	Yes: definite[b]	45	Yes: depression, suicidal	Bifrontal
5 (male)	Yes: hypomania, depression	42	Yes: possible	48	Yes: depression	Unavailable
6 (male)	Yes: mania and depression	56 (ECT)[c]	Yes: probable	68	Family lost in war and history unavailable	Bitemporal > bifrontal
7 (male)	Yes: mania plus psychosis	61	No	61	No	Mild parietal
8 (male)	Yes: mania plus psychosis every 4- to 6-month cycle	63	Yes: probable	70	Yes: depression, C9orf72	Bitemporal
9 (male)	Yes: mania plus psychosis	34	Yes: probable	44	Yes: depression	Bifrontal, bitemporal
10 (male)	No: antisocial, obsessive-compulsive disorder	31	Yes: probable	57	Yes: depression	Bitemporal
11 (female)	Yes: hypomania, depression	Approximately 59	Yes: probable	69	Yes: depression, bipolar disorder	Bitemporal
12 (male)	Yes: mania plus psychosis	62	Yes: definite[d]	66	Yes: depression	Bitemporal > bifrontal
13 (male)	Yes: severe mania	60	No	60	No	Mild temporo-parietal
14 (female)	Yes: mania plus psychosis	55	No	59	No	Normal

[a] C9orf72=chromosome 9 open reading frame 72; FDG=PET=fluorodeoxyglucose positron emission tomography.
[b] Autopsy findings were severe frontotemporal dementia changes (especially right frontal) with tau-positive inclusions in the frontal and temporal neocortex, plus subcortical leukoencephalopathy/hyalinizing arteriopathy (Binswanger's disease) of the arterioles.
[c] ECT was conducted at this age.
[d] Autopsy findings were superficial spongiosis and other frontotemporal dementia changes with tau-positive inclusions in inferior temporal lobes.

for patient 4, as well as for one patient whose psychiatric history could not be verified (patient 6).

DISCUSSION

We found a heterogeneous relationship of bipolar disorder with bvFTD. The symptoms of mania or hypomania and bvFTD have been shown to overlap, and there are reports of manic behavior as an initial manifestation of bvFTD (7, 9–11, 23–25). Given this overlap of symptoms, we examined patients in a bvFTD cohort and found that 10% carried a prior diagnosis of bipolar disorder, far greater than the proposed worldwide prevalence for bipolar spectrum disorders of 2.4% (26). On further analysis of their psychiatric histories, only 11 (8%) patients met criteria for bipolar disorder; among these, three had nonprogressive bvFTD phenocopies (20, 21). The results suggest that late-onset bipolar disorder can be a prodrome of bvFTD and also lead to cognitive or behavioral changes that mimic bvFTD.

Investigators have established manic or manic-like symptoms as potential presenting features of bvFTD (6, 9, 11, 27). There are reports of manic behaviors specifically with bilateral (right >left) temporal lobe degeneration in bvFTD, even with relative sparing of the frontal lobes (6, 28–30). Other reports have described secondary mania from strokes and neurological lesions involving the right inferolateral frontal and basotemporal regions (29, 31, 32). Hence, manic symptoms and bvFTD may share a common neuroanatomical dysfunction, pointing to a potential link between bipolar disorder and this dementia (33, 34).

Bipolar disorder may be a prodrome to bvFTD. Among the major psychiatric syndromes, bipolar disorder is most frequently associated with dementia (35); among major dementias, bvFTD is most commonly preceded by psychiatric symptoms (7). Although a recent meta-analysis of longitudinal (1–9 years) studies did not find significant differences in rates of cognitive decline between patients with bipolar disorder and control subjects (36), many other studies from around the world have reported an increased risk of dementia among cohorts of patients with bipolar disorder, particularly those with bipolar I disorder (37, 38), compared with control subjects, with hazard ratios ranging from 2.36

TABLE 2. Studies assessing bipolar disorder and behavioral variant frontotemporal dementia (bvFTD)

Study	Objective	Patients and study methods	Results	Conclusions
Cerami et al. (72)	Investigating frontotemporal dementia with *GRN* mutation and preceding bipolar disorder symptoms	Two patients (males, N=2; age 57–60s) with *GRN* mutation	Both patients with years of preceding emotional dysregulation or dysphoric hypomania and depressive episode appearing in mid-life	Possible bipolar disorder prodrome phase preceding frontotemporal dementia
Dols et al. (47)	Investigating patients with bipolar disorder with late-life bvFTD mimic	Case report: bvFTD-like syndrome in four patients (males, N=4; ages 62–78) with long-standing bipolar disorder	Diagnosis of bipolar I disorder for ≥10 years; late apathy, disinhibition, loss of empathy and insight, repetitive behaviors, and mild executive dysfunction; nonprogressive for 3–7 years; normal imaging, nondiagnostic CSF, and negative C90rf72	Nonprogressive bvFTD mimic in some patients with long-standing bipolar disorder
Floris et al. (71)	Investigating long-standing bipolar disorder preceding bvFTD with a C9orf72 mutation	Case report: recurrent manic symptoms (males, N=42), bipolar I disorder, and subsequent bvFTD with C9orf72 mutation	bvFTD found in patient 22 years (at age 64) after initially presenting with bipolar I disorder; examination revealing repeat expansions of C9orf72 (>70 repeats)	C9orf72 associated with phenotypic variability that may include bipolar disorder
Ibáñez, 2012 (8)	Investigating atypical presentation of bvFTD	Case report	A 44-year-old man with diagnosis of frontotemporal dementia via brain imaging with several years of preceding bipolar symptoms with psychosis	Bipolar disorder as potential prodrome of bvFTD
Kerstein et al. (9)	Investigating bvFTD mimicking bipolar disorder	Case report	A 65-year-old patient with close diagnostic criteria for bipolar disorder and frontotemporal dementia	bvFTD presenting as bipolar disorder
Lai et al. (46)	Comparing psychiatric disorders across dementia subtypes	Aggregated two national databases and estimated 2-year prevalence of mental health disorders across five dementia subtypes, including 1,181 patients with bvFTD	About 25% of patients with at least one mental health disorder, with a 2-year prevalence reaching 30%–45% in patients with frontotemporal dementia; frontotemporal dementia patients exhibiting the highest prevalence of mood (19%), anxiety (20%), and substance use (19%) disorders, as well as suicidal behavior (4%), compared with other subtypes	Mental health disorders (especially mood disorders) common among patients with bvFTD

continued

TABLE 2, *continued*

Study	Objective	Patients and study methods	Results	Conclusions
Lebert et al. (50)	Characterizing dementia in patients with bipolar disorder	Thirteen patients with bipolar disorder (females, N=9; males, N=4); mean age=70.8 (SD=7.7); dementia with 6.1 years (SD=2.8) of follow-up	No criteria for bvFTD met; common executive dysfunction and frontal behavioral syndrome; moderate extrapyramidal symptoms in 10 patients; and functional imaging (10) revealing decreased frontotemporal uptake	May be a specific postbipolar dementia similar to bvFTD in several respects
Masouy et al. (49)	Proposing a potential link between bipolar disorder and dementia	Two patients (males, N=62; females, N=77), each with about 30 years of bipolar I disorder and late-life deterioration	Late cognitive deterioration during the euthymic phase with deficits in attention, verbal memory, executive functions, and behavior plus cerebral abnormalities on imaging	A "specific dementia" in bipolar disorder with similarities to frontotemporal dementia but with only mild worsening
Meisler et al. (70)	Investigating C9orf72 mutation in patients with bipolar disorder	Eighty-nine patients with bipolar disorder screened for C9orf72	One male patient with bipolar disorder (1%) with C9orf72 expansion (14–20 kilobases) inherited from a parent (8.5–20 kilobases) with bipolar disorder who progressed to bvFTD	Possible association of C9orf72 with a form of bipolar disorder progressing to frontotemporal dementia
Monji et al. (10)	Investigating late-onset bipolar disorder with behavior and imaging similar to bvFTD	Case report	Patient with bipolar disorder misdiagnosed as bvFTD due to abnormal behaviors and neuroimaging observations	Possible presentation of bipolar disorder similar to bvFTD
Papazacharias et al. (18)	Investigating two patients with life-long bipolar disorder who developed frontotemporal dementia in later life	Case report: a 56-year-old woman with bipolar I disorder and a 53-year-old man with bipolar II disorder who developed signs and symptoms of FTD spectrum disorders	Declines in cognitive functions and behavioral and neurological signs consistent with frontotemporal dementia spectrum disorders; MRI and functional imaging changes in frontal and temporal areas	Risk for developing frontotemporal dementia before age 60 may be increased by life-long bipolar disorder
Pavlovic et al. (48)	Investigating lifetime bipolar disorder with late-life bvFTD	Case report: a 68-year-old woman with a 35-year history of bipolar I disorder who developed bvFTD	Patient meeting criteria for bvFTD with progressive deterioration, with frontal atrophy on CT and MRI and frontal-temporal hypoperfusion on single-photon emission computed tomography	Bipolar disorder may represent a preclinical phase preceding the onset of FTD
Rubino et al. (19)	Investigating late-onset bipolar disorder evolving into bvFTD in a patient with the *GRN* mutation	Case report: late-onset bipolar disorder (males, N=54) developing bvFTD (age 68 years old) with *GRN* mutation	Initial manic symptoms at age 54 progressing to bipolar disorder at age 55 followed by deterioration with apathy at age 68 and marked PET frontotemporal hypometabolism, with mutation in the *GRN* gene	Late-onset bipolar disorder that developed into bvFTD over time, carrying a mutation in the *GRN* gene

continued

TABLE 2, *continued*

Study	Objective	Patients and study methods	Results	Conclusions
Vorspan et al. (25)	Investigating the association of manic episodes with bvFTD-like clinical changes	Case report: a 54-year-old woman with bipolar I disorder diagnosed with bvFTD during a manic episode but with neurocognitive improvement afterward	Subsequent relapses associated with cognitive deficits subsiding afterward, despite continued frontal hypoperfusion	Manic episodes may bring out clinical features of bvFTD
Woolley et al. (7)	Investigating rates for psychiatric diagnoses in patients with early neurodegenerative disease	Comparison of rates of psychiatric diagnoses (within 10 years) among patients with bvFTD (N=69), Alzheimer's disease, semantic dementia, and other disorders	bvFTD patients with the most psychiatric diagnoses (50.7%), with eight patients (11.6%) having a diagnosis of bipolar disorder; rate increased by young age, education, and a family psychiatric history	bvFTD patients at high risk of being correctly or incorrectly diagnosed with a prior psychiatric disease

to 7.52 (37, 39–44). The dementia syndrome in these patients may be more similar to bvFTD than other dementias, such as Alzheimer's disease (45). In one large epidemiological study of more than 1,000 patients with FTD, the investigators reported a background of mood disorders in 19% of patients, many with bipolar disorder (46) (Table 2); compared with other major types of dementia, patients with bvFTD are more than twice as likely to have a diagnosis of bipolar disorder (7). Although patients with lifelong bipolar disorder may go on to develop FTD (18), it is late-onset bipolar disorder that carries the most significant risk for developing bvFTD (39, 43). Most of our patients, as well as other study subjects from the literature, exhibited a prodromal relationship of several years between episodes of mania and the development of clinical and FDG-PET evidence of bvFTD (8). Our results, along with those from other studies, suggest that relatively late-onset bipolar disorder can precede typical progressive bvFTD.

Other reports of late-onset bipolar disorder have described the emergence of a nonprogressive bvFTD mimic (10, 47, 48). This is consistent with the bvFTD phenocopy syndrome, which lacks the neuropathology of FTD in most autopsied cases (20, 21). This is also consistent with findings for three of the patients in our study, as well as patients from other studies, with bipolar I disorder who developed bvFTD-like symptoms without progression or neuroimaging changes over subsequent years of follow-up (47). For example, Vorspan et al. (25) described a 54-year-old patient with bipolar disorder with relapsing-remitting agitated manic episodes and symptoms of bvFTD who was followed up for 7 years without progression of symptoms. Severe or numerous manic and depressive episodes may result in frontally predominant cognitive and behavioral injury and an eventual nonprogressive dementia mimic of bvFTD (10, 30, 35, 41, 42, 49, 50). Episodes of mania and depression that are close in time to the onset of the dementia, which was the case for the three nonprogressive patients in our study, may leave a phenotype of bvFTD in their wake, even when euthymic. Patients with bipolar disorder may have relatively stable cognitive changes in executive functions (working memory and cognitive control or cognitive flexibility and response inhibition) and verbal memory (4, 51–53), and most routine executive function tests may fail to distinguish the cognitive changes of bipolar disorder from bvFTD (54, 55). The etiology of cognitive changes from manic or depressive episodes could be due to accelerated aging in cognitive control processes (40, 56–58), prefrontal structural or functional abnormalities (59–62), injury from neuroinflammatory activity or oxidative stress (63, 64), frontal lobe and posterior white matter abnormalities (65–67), or alterations in connectivity, networks, or interoceptive circuits (64, 68).

A third but apparently rare association of bipolar disorder with bvFTD is through a common genetic predisposition. Among patients with familial bvFTD, psychiatric symptoms are the initial manifestations for up to one-half of individuals with the C9orf72 mutation, a nucleotide repeat disorder, and one-quarter of those with a progranulin (*GRN*) mutation, with decreased progranulin levels (1, 69). Some investigators have found a history of bipolar disorder and subsequent bvFTD with C9orf72 (70, 71), similar to one of our patients, and with *GRN* mutations (19, 72). Additionally, some investigators have considered an expanding number of C9orf72 nucleotide repeats in familial bipolar disorder and psychosis leading to bvFTD (48, 70, 72, 73), but others have failed to identify a link to bipolar disorder among relatives of patients with the C9orf72 protein or a clear relationship with the number of repeats (74, 75). To our knowledge, there is no reported association with bipolar disorder in microtubular-associated protein tau mutations (76), the third common genetic form of bvFTD. For C9orf72 and *GRN* mutations, the literature raises the hypothesis that the close link between bipolar disorder and bvFTD may have a genetic predisposition but in relation to other factors, either environmental or additional genetic factors, such as variants of the glycogen synthase kinase 3β gene (77).

There are important limitations to this study. First, it is a retrospective review, albeit of carefully evaluated patients referred to a program specializing in bvFTD. Nevertheless, our study is clinical, observational, and descriptive. Hence, there are a number of potential confounding factors to consider, such as selection bias on referral to a specialty clinic. Second, as with any retrospective study in which information is historical, our study is subject to questions of reliability and completeness, which may be particularly a factor for psychiatric and behavioral symptoms. Wherever possible, we compared the secondary reports with hospitalization records available for many of the manic episodes. Another factor is the disproportionate number of males evident in our total sample and present across the different subgroups. Finally, the imaging results of necessity included imaging reports from other institutions and facilities where direct analysis of brain scans was not available.

CONCLUSIONS

The relationship of bipolar disorder with bvFTD is heterogeneous. Manic or hypomanic episodes may indicate a prodrome heralding bvFTD, possibly with early right >left temporal involvement. Late-onset bipolar disorder may also present as a bvFTD mimic or bvFTD phenocopy that is often mild, nonprogressive, and without further cognitive decline or definitive neuroimaging or neuropathological changes. Much less frequently, there appears to be an association of bipolar disorder with a shared genetic predisposition from mutations in the C9orf72, *GRN*, or other genes. These are preliminary conclusions; however, they can lead to more research on the concepts of a late-onset bipolar disorder prodrome of bvFTD and late-onset bipolar disorder leaving a nonprogressive bvFTD phenotypic profile.

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