Late life bipolar disorder evolving into frontotemporal dementia mimic

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Objectives: Although bipolar disorder has been understood classically as a cyclic disease with full recovery between mood episodes, in the last decade, evidence has accumulated supporting progressive features. The clinical picture of advanced or end-stage bipolar disorder is heterogeneous with possible deficits in cognition and behavior, as illustrated by our case series.

Cases: From our neuropsychiatric outpatient clinic, we describe four cases with bipolar disorder gradually developing a clinical syndrome, including apathy, disinhibition, loss of empathy, stereotypical behavior, and compulsiveness, fulfilling the criteria for possible behavioral variant frontotemporal dementia. All cases were diagnosed with bipolar 1 disorder at least 10 years before the onset of the current symptoms, which were not due to recent mood episodes or switches of medication. In all cases, 3–7 years of follow-up yielded no progression. Repeated neuroimaging was within normal limits. Cerebrospinal fluid biomarker studies were not supportive of underlying neurodegenerative pathology. C9orf72 mutation status was negative in all cases.

Conclusion: Symptoms fitting the criteria for possible behavioral variant frontotemporal dementia may be present in end-stage of bipolar disorder. An alternative neurodegenerative nature seems unlikely based on repeated normal neuroimaging and the absence of clinical progression. Functional involvement of the frontal-subcortical networks might play a role.

Keywords: bipolar disorder, older, staging, bvFTD, benign phenocopy syndrome

Introduction

Although bipolar disorder has been classically considered a cyclic disease with full recovery between mood episodes, in the last decade, evidence has accumulated supporting the notion that bipolar disorder is a progressive condition with functional decline over time. In older patients with bipolar disorder, several studies have confirmed a significant cognitive dysfunction that was not associated with mood or prodromal phase of dementia.2–6 Similarly, magnetic resonance imaging (MRI) findings in older bipolar patients have shown regional gray matter volume reduction and white matter hyperintensities7–10 that were not consistent with a dementia profile but hypothesized to be correlated with disease duration11 or a result from the toxic effects of recurrent mood episodes.12 The cognitive dysfunction and mild structural brain alterations seen in patients with bipolar disorder suggest a model of accelerated aging.13–16 The clinical stages of bipolar disorder can range from a latent or asymptomatic form (stage 0) to a chronic, end-stage presentation (stage IV). Accelerated aging defines the later stages of bipolar disorder.14–16 The clinical picture of end-stage bipolar disorder is heterogeneous with possible cognitive and behavioral deficits. Here, we report a series of four male cases diagnosed with bipolar disorder who subsequently developed gradually progressive behavioral and social-emotional changes rather similar to behavioral variant...
frontotemporal dementia (bvFTD). A neurodegenerative nature of this condition, however, could not be demonstrated after 3–7 years of extensive clinical follow-up. We propose that a nonprogressive frontal lobe syndrome constitutes a possible manifestation of end-stage bipolar disorder.

Cases
The Medical Ethical Committee of the VU Medical Centre, Amsterdam, approved the study. All patients provided written informed consent to publish patient data. As a tertiary neuropsychiatric center, we have specialized in diagnosis of patients presenting with behavioral symptoms in later life. All patients undergo a psychiatric, neurological, and neuropsychological examination and an MRI scan at initial presentation. Most patients also undergo a lumbar puncture with determination of cerebrospinal fluid (CSF) biomarkers for neurodegeneration. In each case, a consensus diagnosis is made by a neurologist and a psychiatrist with consecutive follow-up. As we have no possibilities for outreaching care, most of our patients are treated by local mental health organizations or memory clinics. Here, we describe four cases, all alive after a follow-up of 3–7 years.

Case 1
A 78-year-old male, diagnosed with bipolar 1 disorder at the age of 18, was referred to our memory clinic because of gradually progressive behavioral change. Although the patient had no complaints, his wife described changes starting several years ago consisting of excessive consumption of cheese, diminished empathy, and sitting on the couch all day smoking excessively. Over the years, he began to masturbate in public and demonstrated excessive clock watching. He lost the ability to spontaneously initiate conversations and echoed other people’s words. Over time, he developed urinary and fecal incontinence due to personal neglect. His family history revealed a brother with schizophrenia and several first degree family members with depression (Table 1).

He had previously been admitted three times, but his mood had been stable for over 10 years with use of lithium and zuclopentixol. There was no concurrent mood or psychotic symptoms. Lithium serum levels were within the therapeutic range (0.4–0.8 mmol/L) and a dose reduction did not change his behavior. Mild extrapyramidal features on the neurological examination were attributed to medication use. With respect to cognitive performance, memory problems were not reported, but his spatial orientation was impaired. Mini-Mental State Examination (MMSE) was 27/30 and frontal assessment battery (FAB) was 14/18. At neuropsychological examination, a predominant executive dysfunction was found. Repeated MMSE and FAB scores were 29/30 and 12/18, respectively, after 5 years. Repeated MRI of the brain yielded no abnormalities and [18F]-2-deoxy-2-fluoro-d-glucose positron emission tomography (FDG-PET) scans were repeatedly normal. CSF levels of tau and phosphorylated tau were slightly elevated, with normal CSF level of amyloid beta-42. There were no mutations found in the Microtubule-Associated Protein Tau (MAPT)-gen, progranulin (GRN)-gen, or Presenilin-1 protein (PSEN1)-gen, nor a repeat expansion in the chromosome 9 open reading frame 72 (C9ORF72)-gen. After 7 years of follow-up at our memory clinic, it was concluded that this very slowly progressive frontal lobe syndrome was not due to bipolar mood symptoms or a neurodegenerative disease, such as bvFTD.

Case 2
A 70-year-old male attended our memory clinic because of forgetfulness and word-finding difficulties of 4 years’ duration. He had been diagnosed with bipolar 1 disorder 17 years ago after a serious suicide attempt and successfully stabilized with lithium (Table 1). Three years ago, these same memory complaints made him discontinue lithium abruptly, and a depressive relapse followed. At initial memory clinic presentation, he was on carbamazepine and mirtazapine, without any significant mood symptoms. His wife and daughter reported a gradual change of behavior while his mood was euthymic. He became more focused on religion, impulsively bought a car, and lived by a rigid daily routine. Moreover, inappropriate social behavior was reported, such as visiting the swimming pool without his dentures. There was a gradual loss of empathy. His family history was negative for psychiatric disorders, but positive for dementia in two grandmothers.

On examination using standardized rating scales, his MMSE was 25/30 and FAB 12/18. He exhibited a moderate score on the stereotypy rating scale (SRI 8/60). Repeated neuropsychological examination revealed nonprogressive mild executive and episodic memory disturbances with decreased mental speed. His MMSE was 29/30 after 6 years, with a FAB score of 17/18. MRI scans of the brain were repeatedly within the normal range for his age. CSF levels of amyloid beta-42, tau, and phosphorylated tau were all within the normal range. After a follow-up of 6 years, his behavior remained stable and could not be attributed to bipolar mood symptoms or a neurodegenerative disease, such as bvFTD.

Case 3
A 65-year-old male reported no complaints when visiting a memory clinic, although he admitted that he had always been controlling and compulsive, with an urge of excessive cleaning. He had been diagnosed with bipolar disorder and
obsessive compulsive personality disorder more than 10 years ago and had been stable on a MAO inhibitor (Table 1). In the last year, he experienced vivid visual hallucinations that initially started during acute medical illness (repeated bout of pneumonia) but persisted after resolution of the medical events at night. His wife and daughter reported increased obsessive compulsive behavior with verbal aggression toward strangers if his routine got disturbed. Furthermore, he tried to force his wife to excessively buy items and was increasingly snacking. His daughter noticed that he had very little interest in others and did not take initiative in social contact nor did he seem to notice the needs of others. His family history was

| Characteristics of the four cases | Case 1 | Case 2 | Case 3 | Case 4 |
|----------------------------------|--------|--------|--------|--------|
| Clinical and sociodemographic characteristics | | | | |
| Age (years) | 78 | 70 | 65 | 62 |
| Sex | Male | Male | Male | Male |
| Education in years | 6 | 11 | 13 | 13 |
| Age at onset bipolar disorder (years) | 18 | 53 | 51 | 28 |
| Number of admissions | 3 | 1 | 2 | >2 |
| Family history (First degree) | Psychiatry | Cardiovascular | Cardiovascular | Cardiovascular |
| Somatic history | Diabetes | Myocardial infarction | Chronic obstructive pulmonary disease | Diabetes |
| Psychopharmaca | Lithium 800 mg Zuclopentixol 6 mg | Lithium 1,200 mg | Quetiapine 400 mg Phenelzine 45 mg | Temazepam 20 mg Oxazepam 50 mg |
| Rasovsky criteria | | | | |
| Disinhibition | + | + | + | + |
| Apathy | + | + | + | + |
| Loss of empathy | | | + | + |
| Stereotypical behavior | + | + | + | + |
| Eating behavior | + | + | + | + |
| Executive dysfunction | + | + | + | + |
| Neuropsychology | | | | |
| MMSE at presentation | 28 | 25 | 27 | 28 |
| MMSE after follow-up | 29 | 29 | 23 | 29 |
| FAB | 14 | 12 | 18 | 17 |
| FAB after follow-up | 12 | 17 | 15 | 18 |
| Mental speed/attention | Slightly decreased | Slightly decreased | Decreased | Normal |
| Executive tasks | Mildly disturbed | Mildly disturbed | Mildly disturbed | Normal |
| Episodic memory | Normal | Mildly disturbed | Normal | Normal |
| Semantic memory | Normal | Mildly disturbed | Normal | Normal |
| (category fluency) | | | | |
| Visuospatial functions | Normal | Normal | Normal | Normal |
| Language | Normal | Normal | Normal | Normal |
| Social cognition | | | | |
| Social cognition profile (faux pas, Eckman faces) | n/a | Impaired, no recognition of faux pas, impaired recognition of disgust | Impaired, no recognition of faux pas, impaired recognition of disgust | Impaired recognition of sadness |
| Biomarkers | | | | |
| MRI: Fazekas | 1 | 1 | 0 | 0 |
| MRI: MTA | 0/0 | 1/1 | 0/0 | 1/1 |
| MRI: GCA | 0 | 1 | 0 | 0 |
| FDG-PET | Normal | n/a | Normal | Normal |
| PIB-PET | n/a | n/a | Normal | n/a |
| CSF: amyloid beta-42 (≥ 550 pg/mL) | 1,071 | 632 | n/a | 880 |
| CSF: tau (≤ 375 pg/mL) | 400 | 202 | n/a | 486 |
| CSF: P-tau (≤ 52 pg/mL) | 58 | 36 | n/a | 66 |

Abbreviations: CSF, cerebrospinal fluid; FAB, frontal assessment battery; FDG-PET, [18F]-2-deoxy-2-fluoro-D-glucose positron emission tomography; GCA, global cortical atrophy; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MTA, medial temporal lobe atrophy; +, present; n/a, not applicable; PIB-PET, Pittsburgh compound B positron emission tomography; P-tau, phosphorylated tau.
negative for psychiatric disorders and dementia. At neurological examination, there were no extrapyramidal signs. His MMSE was 27/30 and FAB 18/18. He had a high score on stereotypical symptoms (SRI 20/60), which according to his family could not be attributed to his premorbid personality. Repeated neuropsychological examination revealed very slowly progressive mild executive disturbances with decreased mental speed, with MMSE 23/30 and FAB 15/18. His MRI scans showed nonprogressive frontoparietal atrophy after 3 years of follow-up, while his FDG- and Pittsburgh compound B-PET scans were completely normal. His behavioral symptoms could not be accounted for by obsessive compulsive personality disorder, bipolar mood symptoms, or a progressive neurodegenerative disorder.

Case 4
A 62-year-old male visited our memory clinic with progressive memory complaints. He noticed word-finding difficulties and using wrong words. He had been diagnosed with bipolar 1 disorder 30 years ago and had been hospitalized for bipolar mania 6 months before his memory complaints started (Table 1). His mood was euthymic and controlled with lithium and olanzapine. Lithium serum levels were within the therapeutic range (0.4–0.8 mmol/L) and reducing the dose did not change his behavior. According to his wife, he frequently misspelled words and his speech had slowed. After recovery from his mania, his social judgment remained impaired (eg, asking a 6-year-old unknown girl to accompany him on a canoe trip, talking excessively during a funeral speech, making personal comments to female strangers). His family history was negative for psychiatric disorders or dementia. Except the presence of a mildly slurred speech, no neurological abnormalities were present. At repeated neuropsychological examination, there were no disturbances, with an initial MMSE 28/30 and FAB 17/18. His MRI scan showed medial temporal atrophy grade 1 on both sides without any other abnormalities, and his FDG-PET was within normal range. His CSF had normal amyloid beta-42 (880 pg/mL), with slightly elevated tau and phosphorylated tau (486 and 66 pg/mL, respectively). After 3 years of follow-up, his mood remained stable. His wife reported that he had regained some of his empathy, but was not at his usual level of concern for others. His speech impairments remained static. Repeated MMSE and FAB scores were 29/30 and 18/18, respectively. A repeated MRI scan after 2 years showed no increase of atrophy. His changed behavior could not be accounted for by progressive neurodegenerative disorder after 3 years of follow-up.

Discussion
We present four older male patients with early- and late-onset bipolar disorder who had behavioral and functional impairment consistent with a frontal lobe syndrome. Their informant-based report suggested that this condition was clinically distinct from symptoms characteristic of these individuals’ previous manic or depressive symptoms. After screening for cognitive and executive deficits, few impairments were found, as shown by relatively high MMSE and FAB scores. At neuropsychological testing, there was only mild impairment in mental speed and executive functions. Most profound was their lack of insight and empathy. All four displayed disinhibition and stereotyped behavior, whereas apathy was a significant feature in two cases. All cases fulfilled the Rascovsky criteria for “possible” bvFTD; however, after 3 to 7 years of follow-up, there was no progression to “probable” bvFTD since no significant functional decline over time or progressive frontotemporal deficits on neuroimaging developed.

In these cases, the age-related MRI findings and absence of cognitive deficits in multiple domains suggest no comorbid dementia, although we cannot entirely rule out case 2 as having early-stage dementia. Although white matter hyperintensities are frequently reported in older bipolar patients, our cases had low Fazekas scores, indicating that their clinical profile was not related to vascular pathology. Two cases had slightly elevated tau levels suggestive of axonal degeneration. However, their normal amyloid beta-42 levels and lack of progressive deterioration make a neurodegenerative cause unlikely.

A similar clinical picture with emotional blunting after manic-depressive episodes has been described in the early 20th century as “dementia maniaco-depressionis”. The clinical picture described here does not appear to be just a result of pharmacotherapy. Furthermore, with an average of two admissions in our patients and a disease duration ranging from 14 to 60 years, it is not possible to link presumed toxic effects of mood episodes to their current symptoms.

A proportion of bvFTD patients have a slow course with relatively normal neuroimaging, particularly those carrying a C9orf72 repeat expansion. This repeat expansion has been found in patients with bipolar disorder preceding FTD, however, this mutation was not detected in a cohort of 206 patients with bipolar disorder. C9orf72 mutations were excluded as a possible cause of the clinical syndrome in our cases.

Deficits in emotion recognition and theory of mind have been recognized as hallmarks of bipolar disorder.
Moreover, they have been reported as an early phenomenon in bvFTD. Executive disturbances are the most prominent feature in the neuropsychological examination in bvFTD, however executive impairment is common in elderly patients with bipolar disorder as well.

A possible link between bipolar disorder and bvFTD has also been suggested by case reports on patients presenting with manic symptoms as a first manifestation of bvFTD and patients with a lifetime diagnosis of bipolar disorder evolving into bvFTD. This large clinical overlap in social cognition, executive disturbances, and behavioral profiles might be explained by the involvement of common functional neuroanatomical networks.

The condition fulfilling criteria for possible bvFTD failing to convert to probable bvFTD over time is labeled benign bvFTD phenocopy syndrome. These patients exhibit behavioral and functional impairments consistent with a frontal lobe syndrome but fail to progress over time and have no frontal or anterior temporal atrophy or hypoperfusion at follow-up. Although an alternative explanation is generally lacking in these cases, end-stage bipolar disorder may be one of the underlying causes of this syndrome, with a male predominance as in our cases.

Conclusion
To the best of our knowledge, there have been no previous case series of older patients with bipolar disorder illustrating progressive behavioral change culminating in frontal lobe syndrome. In all four cases, behaviors could not be attributed to bipolar mood symptoms and were reported as a distinct loss of insight and empathy with disinhibition and socially inappropriate behavior. In spite of the limitations imposed by our small sample size, confined psychiatric follow-up, and lack of postmortem evaluation to rule out other pathological explanations, the clinical implications of our case series are potentially valuable. The recognition of this phenotype is important for the understanding of brain–behavior relationships, in particular, the pathophysiology of bipolar disorder. Our case series is a reminder that clinicians should reject a diagnosis of bvFTD in patients with bipolar disorder in the absence of obvious clinical and radiological progression over time.

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Disclosure
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