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The overlap of symptomatic dimensions between frontotemporal dementia and several psychiatric disorders that appear in late adulthood

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Abstract
Several factors make diagnosis of a possible behavioural variant of frontotemporal dementia (bvFTD) particularly challenging, especially the overlap of certain symptomatic dimensions such as apathy, disinhibition, depression, anhedonia, stereotyped behaviour, and psychosis between bvFTD and several psychiatric disorders that appear in late adulthood. We discuss the most frequent psychiatric conditions that can simulate early bvFTD symptoms, including late onset bipolar disorder, late onset schizophrenia-like psychosis, late onset depression, and attention deficit hyperactivity disorder in middle and older age.

Introduction

Behavioural variant frontotemporal dementia (bvFTD) is a neurodegenerative disease characterized by progressive changes in behaviour and personality associated with frontal and anterior temporal lobe atrophy. Behavioural changes may include disinhibition, social inappropriateness, compulsions, loss of insight, loss of empathy, excessive jocularity, gluttonous overeating, and impaired moral decision-making. Impairments in the contextual integration of multiple social clues in different cognitive domains are frequently observed (Ibáñez & Manes, 2012). Patients with bvFTD may also present mood disturbances including apathy, euphoria, and irritability. These changes generally appear in the earlier stages of the disease and are best recognized by the closest relatives, friends or colleagues, usually preceding the onset of cognitive deficits. The appropriate clinical diagnosis of bvFTD can be difficult and can represent a real challenge. Certain neuropsychiatric symptoms and changes in behaviour and personality, especially when they are very subtle, can be ignored or attributed to a primary psychiatric condition in about half of bvFTD patients (Woolley et al., 2011). This is likely the result of several different factors, one of which is the overlap between the symptomatic dimensions of bvFTD and several psychiatric disorders, especially in the early stages of bvFTD. An international consortium recently developed revised diagnostic criteria for bvFTD organized into a specific diagnostic hierarchy (Table 1), namely possible, probable and definite bvFTD (Rascovsky et al., 2011). The proposed revised guidelines showed better diagnostic accuracy in a bvFTD sample with known FTLD pathology compared to previously established criteria published by Neary and colleagues (1998). The new criteria are supported by optimized diagnostic features and their adoption has major implications in discriminating this disorder from other dementias and psychiatric disorders, as well as from other conditions such as the recently described 'phenocopy syndrome' (Rascovsky et al., 2011). In reference to this latter concept, recent studies have identified a subgroup of individuals who fulfil clinical bvFTD criteria but present a benign course (Davies et al., 2006; Hornberger et al., 2009; Kipps et al., 2007). Such cases are considered to have bvFTD 'phenocopy syndrome', showing distinctive behavioural features without actively progressing to frank dementia (Davies et al., 2006; Kipps et al., 2007). These phenocopy or non-progressive patients present identical clinical features as those seen in actual bvFTD, but have normal brain imaging, better performance on cognitive

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Table 1. New diagnostic criteria for bvFTD. Adapted from Rascovsky et al. (2011).

I. Neurodegenerative disease
The following symptom must be present to meet criteria for bvFTD
- A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant)

II. Possible bvFTD
Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events
- A. Early* behavioural disinhibition; one of the following symptoms (A1–A3) must be present:
  - A1. Socially inappropriate behaviour
  - A2. Loss of manners or decorum
  - A3. Impulsive, rash or careless actions
- B. Early apathy or inertia; one of the following symptoms (B1–B2) must be present:
  - B1. Apathy
  - B2. Inertia
- C. Early loss of sympathy or empathy; one of the following symptoms (C1–C2) must be present:
  - C1. Diminished response to other people´s needs and feelings
  - C2. Diminished social interest, interrelatedness or personal warmth
- D. Early perseverative, stereotyped or compulsive/ritualistic behaviour; one of the following symptoms (D1–D3) must be present:
  - D1. Simple repetitive movements
  - D2. Complex, compulsive or ritualistic behaviour
  - D3. Stereotypy of speech
- E. Hyperorality and dietary changes; one of the following symptoms (E1–E3) must be present:
  - E1. Altered food preferences
  - E2. Binge eating, increased consumption of alcohol or cigarettes
  - E3. Oral exploration or consumption of inedible objects
- F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions; all of the following symptoms (F1–F3) must be present:
  - F1. Deficits in executive tasks
  - F2. Relative sparing of episodic memory
  - F3. Relative sparing of visuospatial skills

III. Probable FTD
All of the following symptoms (A–C) must be present to meet criteria
- A. Meets criteria for possible bvFTD
- B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)
- C. Imaging results consistent with bvFTD; one of the following (C1–C2) must be present:
  - C1. Frontal and/or anterior temporal atrophy on MRI or CT
  - C2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioural variant FTD with definite FTLD pathology
Criterion A and either criterion B or C must be present to meet criteria
- A. Meets criteria for possible or probable bvFTD
- B. Histopathological evidence of FTLD on biopsy or at post-mortem
- C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD
Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.
- A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
- B. Behavioural disturbances are better accounted for by a psychiatric diagnosis
- C. Biomarkers strongly indicative of Alzheimer´s disease or other neurodegenerative process

*As a general guideline 'early' refers to symptom presentation within the first 3 years.

measures, and relative sparing of activities of daily living (ADL). Although the aetiology of phenocopy patients remains unknown, it would seem unlikely that these individuals have a neurodegenerative process in light of systematic normal brain imaging even many years after onset of the symptoms, the lack of clinical progression when under medical review, and within normal neuropsychological and ADL performance (Kipps et al., 2010). We consider the hypothesis that many of these phenocopy cases could be the expression of atypical psychiatric disorders affecting adults in their older age. These conditions include, but may not be limited to late onset bipolar disorder, late onset depression, late onset schizophrenia-like psychosis, chronic attention deficit hyperactivity disorder, obsessive–compulsive disorder, alcohol abuse and the exacerbation of a pre-existing personality disorder (Manes et al., 2010), although, based on our clinical experience, personality disorders tend to stabilize through time

and would not constitute a solid differential diagnosis of bvFTD in late adulthood. Accordingly, we claim that in order to provide an accurate diagnosis of frontotemporal dementia, it is essential that trained psychiatrists with experience in late life mental disorders evaluate and exclude these psychiatric conditions, especially in patients without a clear frontal involvement on brain imaging (Manes, 2012). Here, we discuss the clinical characteristics of the most frequent psychiatric conditions that should be excluded when considering a diagnosis of phenocopy syndrome or possible bvFTD.

Late onset bipolar disorder

Bipolar disorder (BD) is a recurrent episodic illness characterized by alternating episodes of depression and mania or hypomania. The increase in life expectancy among the general population in recent years may have led to the emergence of a growing number of late onset BD cases, hence consolidating an emerging interest for this illness (Zung et al., 2009). Most research studies refer to 'late onset' BD as being diagnosed at age 50 or older, but there is no clear agreement on this definition (Sajatovic et al., 2005). Although there is evidence that the frequency of new onset BD declines with advanced age (Depp & Jeste, 2004), it was observed that 6–8% of all new cases develop in individuals 60 years or older (Almeida & Fenner, 2002; Sajatovic et al., 2005). Elderly bipolar individuals constitute a heterogeneous population representing at least two groups: early onset patients who have aged (who experienced their first mood episode in their early adulthood) and late onset patients (who develop their illness at an older age). It is essential to distinguish between older BD patients by age at onset because late onset patients show a less frequent family history of affective disorders and higher frequency of neurological co-morbidities compared with early onset patients, suggesting the hypothesis that there may be an influence of non-genetic aetiological factors within this subgroup (Depp & Jeste, 2004; Martino et al., 2012; Schürhoff et al., 2000; Shulman & Post, 1980). In fact, a greater prevalence of vascular risk factors (Cassidy & Carrol, 2002) and higher prevalence of silent cerebral infarctions (Fujikawa et al., 1995) has been reported in patients with late onset BD compared with patients with early onset of the disease (Martino et al., 2012).

An association between increased age at onset and increased episode duration or chronicity has also been reported (Young, 1997). Some studies found that patients with late onset of the disease presented more affective episodes per year (Zung et al., 2009) and had more extensive and severe neurocognitive impairments than those with early onset (Martino et al., 2012), especially in psychomotor performance and mental flexibility (Schouws et al., 2009). Even patients meeting criteria for euthymia present persistent impairments in verbal memory, executive functions (Delaloye et al., 2009; Martino et al. 2008) and social cognition (Ibáñez et al., 2012a; Ibáñez et al., 2012b). Nevertheless, as seen in certain bvFTD patients, some studies suggest that at least a subgroup of euthymic bipolar patients demonstrate intact executive functioning in classic neuropsychological tests, which could be due to the lack of ecological validity, that is, the ability of a task to pose real-life-like demands (Torralva et al., 2012a). This tendency to present chronic rather than episodic affective symptoms and the presence of impaired executive functions can represent, in some cases, a real challenge for making a differential diagnosis with FTD.

Neuroimaging research studies found that older people with BD may show increased signs of atrophy and cerebral vascular lesions compared with normal age-matched control subjects (Fujikawa et al., 1995; Rabins et al., 2000). The brain lesions more frequently associated with late onset BD were subcortical hyperintensities, decreased cerebral blood flow, and silent cerebral infarctions (Tamashiro et al., 2008).

It is interesting to analyse what happens in bipolar patients as they age. It was observed that the prevalence of dementia in older people with BD seems to increase according to the number of manic episodes (Kessing et al., 2004). Even bipolar type VI was proposed to describe patients that present cognitive decline and frequent mood instability, often with mixed or depressive features, as the manifestation of late onset bipolarity (Ng et al., 2008). These authors suggested that dementia releases latent bipolarity in individuals with certain predispositions, such as affective temperaments. The term 'temperament' refers to the emotional domain of personality. The affective temperaments (including different types such as cyclothymic, hyperthymic, depressive, irritable and anxious) are considered to be the subclinical manifestations and frequently the precursors of the bipolar or unipolar major mood disorders (Akiskal, 1995; Rihmer et al., 2010; Vázquez et al., 2008).

Therefore, even in cases in which organic disorders and particularly dementia are in the foreground, bipolarity has to be explored in depth, as it may guide therapeutic decisions. This could be achieved by looking for the existence of premorbid affective temperament, the notion of previous behaviour with negative psychosocial consequences, and the presence of a family history of affective disorders (Dorey et al., 2008). The diagnosis of bipolarity may be easier when late onset mania has been preceded by depressive episodes.

Late onset schizophrenia

Schizophrenia is a mental illness characterized by the presence of positive symptoms (delusions, hallucinations and thought disorders), negative symptoms (affective flattening, poor speech, anhedonia), affective symptoms (dysphoria, anxiety, agitation) and cognitive impairment (Charlish & Cutting, 1995; Heinrichs & Zakzanis, 1998). It usually strikes in adolescence or early adulthood, but may arise for the first time in middle or late life.

The emergence of schizophrenia in late life remains a controversial issue. The proportion of patients with schizophrenia whose illness first emerged after the age of 40 has been estimated to be 23.5% (Harris & Jeste, 1988). An expert consensus (Howard et al., 2000) reviewed the literature on late onset psychosis and coined the terms of 'late onset schizophrenia' (illness onset after 40 years of age) and 'very late onset schizophrenia-like psychosis' (onset after 60 years).

It has been observed that late onset patients are more likely to develop visual, tactile and olfactory hallucinations, persecutory delusions and third person, running commentary and accusatory or abusive auditory hallucinations compared with early onset patients (Howard et al., 1993; Pearlson et al., 1989); they are also less likely to display formal thought disorder, affective flattening or blunting (Howard et al., 1993; Pearlson et al., 1989). When onset of psychosis is after age 60, formal thought disorder and negative symptoms are very rare (Almeida et al., 1995; Howard et al., 1994).

Regarding differential diagnosis between late onset schizophrenia and bvFTD, it is well established that delusions and hallucinations are very frequent in schizophrenia (APA, 2000) but they are not commonly described in bvFTD (Ibach et al., 2004; Le Ber et al., 2006; Mendez et al., 2008), although a high rate of visual hallucinations has been reported in individuals with FTD and progranulin (PGRN) gene mutations (Le Ber et al., 2008), and more recently an association between FTD patients with C9ORF72 mutations and the presence of psychosis was found (Snowden et al., 2012). However, there are symptoms such as echolalia, aprosody of speech, echopraxia, primitive reflexes, utilization behaviour, 'negative' symptoms, self-neglect, and bizarre, compulsive, impulsive and stereotyped behaviours that may be recognized in both disorders (Velakoulis et al., 2009), although in bvFTD patients, these symptoms are more frequent in the later stages of the disease. Impaired executive functions with relative preservation of visual perception and spatial skills (Pantelis et al., 1997; Snowden et al., 2002) and deficits in social cognition, theory of mind, emotion detection and recognition, as well as empathy, have also been identified in both disorders (Amoruso et al., 2012; Gleichgerrcht et al., 2010a; Gleichgerrcht et al., 2011; Huepe et al., 2011; Ibáñez et al., 2011a; 2011b; Lough et al., 2006; Riveros et al., 2010; Shamay-Tsoory et al., 2007).

Neuroimaging studies are a common procedure in first psychotic episode, mostly in late onset cases, and this could certainly help in arriving at an appropriate diagnosis (Waddington, 2007). Structural brain imaging typically shows marked frontotemporal atrophy in bvFTD (Hornberger et al., 2010), whereas in schizophrenia, the most consistent finding includes ventricular enlargement and slight to moderate deficits in the superior temporal gyrus and medial temporal lobe structures (Shenton et al., 2001). In functional imaging studies using SPECT or PET, the decrease in frontotemporal perfusion and metabolism in schizophrenia is not as consistent a finding as in bvFTD (Hu et al., 2010). Nevertheless, a meta-analysis has supported hypofrontality in patients with schizophrenia both at the resting state and when performing cognitive tasks involving the frontal cortex (Hill et al., 2004).

Differential diagnosis between schizophrenia and bvFTD could be a hard task. It is crucial to thoroughly know the onset and progression of symptoms and the patient's history, both personal and familiar. For example, the presence of an explicit psychotic disorder well before the onset of certain symptoms such as disinhibition, silly jokes, reclusion, apathy and loss of interest for activities, could be helpful in guiding the diagnosis of a possible schizophrenia-like psychosis.

Late onset depression

Late onset depression (i.e. after age 65) is a potentially impairing condition that is frequently underdiagnosed. If not properly treated, the disease may persist for months and bring about changes associated with poor quality of life, social functioning impairments, and low adherence to treatment with worsening of chronic health conditions (Katon, 2003).

The prevalence of major depression is approximately 2% among the elderly (Blazer et al., 1991; Reynolds, 1992), a figure that increases to 12% in patients living in residential homes, and up to 30% when considering subsyndromic forms of depressive symptoms (Foster et al., 1991; Parmelee et al., 1991).

It is well known that depression in geriatric populations is more somatic than ideational. Patients usually report somatic complaints, hypochondria, insomnia, and apathy symptoms (lack of interest and motivation), but sadness, loss of hope and wreck are less frequent (Avery & Silverman, 1984; Brown et al., 1984). It is usual for depression to present

co-morbidly with other psychiatric disorders such as anxiety, personality disorders and substance abuse (more frequently, alcohol) (Callahan et al., 1994; Gum & Cheavens, 2008; Speer & Bates, 1992). Several authors have found that reduced insight is not uncommon among these patients (Ghaemi et al., 2000; Yen et al., 2005).

Over half the patients with late onset depression present severe cognitive impairment (usually performance below the tenth percentile of controls) (Butters et al., 2004). Memory, attention, and executive functions are most severely affected, which are indicative of prefrontal and temporal lobe dysfunction, as well as subcortical circuitry (Lockwood et al., 2000; Rapp et al., 2005). These patients often exhibit diminished processing speed and more profound executive impairment relative to patients with early onset depression (Butters et al., 2004; Hermann et al., 2007; Sheline et al., 2006). Many studies support the evidence that late onset depression with associated cognitive impairment may be a prodromal illness for dementia, either Alzheimer's disease or vascular dementia in the majority of patients (Alexopoulos et al., 1993; Schweitzer et al., 2002).

There are now multiple reports in the literature suggesting the existence of one type of late onset depression with distinctive clinical features that has been strongly associated with cerebrovascular disease. This entity has been referred to as 'vascular depression' and stipulates that depending on the type of cerebrovascular disease and its neural substrate, it will predispose, precipitate, or perpetuate certain depressive syndromes in geriatric populations (Alexopoulos et al., 1997). Vascular depression seems to develop following the involvement of frontal systems or some of their modulating pathways (Alexopoulos et al., 1997). These patients exhibit marked cognitive impairment, especially in their executive functioning, and psychomotor delay, accompanied by reduced depressive ideation, diminished agitation and guilt feelings, and reduction of insight relative to non-vascular depressive patients (Alexopoulos et al., 1997; Baldwin & O´Brien, 2002).

Neuroimaging usually reveals basal ganglia abnormalities and white matter hyperintensities on MRI, which have been described by some authors as 'periventricular hyperintensities, deep white matter hyperintensities, leukoencephalopathy or leukoaraiosis' (Hachinski et al., 1987; Mirsen et al., 1991). Vascular depression symptoms are consistent with lesions involving striatal-pallidal-thalamic-cortical pathways and other areas (Alexopoulos et al., 1997; Naarding et al., 2006).

Reported prevalence of depression in bvFTD varies considerably depending on the instrument employed to measure mood symptoms, but it is estimated that prevalence is lower than in Alzheimer´s disease (Barber et al., 1995; Mendez et al., 1998). Depression in bvFTD patients shares some atypical characteristics with late onset depression, such as irritability, reduced motivation and lack of energy, psychomotor retardation, and poor depressive ideation (Lopez et al., 1996). But when depressive symptoms manifest in bvFTD, they usually do so accompanied by other symptoms such as inappropriate behaviour, disinhibition, irritability, obsessive–compulsive symptoms, and eating behaviour disorders, among others.

Cognitively, both pathologies present with executive impairment, although in patients with bvFTD, executive performance tends to be spared in the early stages when cognitive functioning is relatively preserved.

Among patients with bvFTD, depression is more strongly associated with severe frontotemporal atrophy, especially within the temporal lobe, while emotional disturbances tend to correlate more strongly with early atrophy of right temporal areas (Bozeat et al., 2000; Chow & Mendez, 2002).

It is important to highlight that normal ageing can lead to frontal cortex atrophy (Chow et al., 2008; Raz et al., 1997) and this finding may be present in patients diagnosed with late onset depression. While such findings could make differential diagnosis of bvFTD more challenging, it has been suggested that predominantly left – but not right – atrophy would be more specific for cases of bvFTD and PPA (Chow et al., 2008).

Attention deficit hyperactivity disorder

The challenge of differential diagnosis is not limited to affective or psychotic disorders. For instance, attention deficit hyperactivity disorder (ADHD) is a lifespan disorder characterized by distractibility, hyperactivity, impulsive behaviours and the inability to remain focused on tasks or activities. It is not uncommon for this disorder to be overlooked or misdiagnosed in early childhood and ADHD prevalence studies indicate that about 4% of the adult population suffers from this disorder (Faraone et al., 2003). Although the expression of ADHD in adults resembles the set of symptoms identified earlier in childhood, clinical signs are influenced by the changes that occur as patients grow older (Torralva et al., 2012b). Besides the impaired performance on tests of attention and inhibition, executive functions seem to be the most severely impaired cognitive domain in adult ADHD patients, affecting planning, self-monitoring, working memory, flexibility and set shifting, among others (Torralva et al., 2012b). The dysexecutive profile of ADHD patients is qualitatively, though not always quantitatively, similar to the pattern observed in adults with

frontal lobe damage (Johnson et al., 2001; Shue & Douglas, 1992). Recently, neural correlates of social cognition impairments frequently observed in bvFTD (e.g. face processing and decision-making) have been also reported in ADHD (Ibáñez et al., 2011c, 2012b).

Some previously undiagnosed ADHD patients go undetected until they get older and begin to complain of behavioural and cognitive deficits. Nevertheless, this condition is often neglected in the differential diagnosis in memory clinics (Gleichgerrcht et al., 2010a). As literature is scarce in relation to the aging of these ADHD patients, more studies are needed to clarify this issue.

Conclusion

We propose that certain psychiatric disorders that appear in late adulthood could simulate bvFTD, especially in the early stages of the disease and in those cases without frontotemporal atrophy on neuroimaging. Late life psychiatric disorders and possible bvFTD can share symptomatic dimensions, including apathy, disinhibition, depression, anhedonia, stereotyped behaviour or psychosis, and establishing an appropriate differential diagnosis may be difficult. The lack of family history of mood disorders in late onset mood disorders is evidence that speaks in favour of organic aetiology. Due to the complexity of its diagnosis, we suggest that patients with bvFTD should be evaluated in the context of an interdisciplinary clinical setting involving behavioural neurologists, neuropsychologists, and psychiatrists. An exhaustive psychiatric evaluation is suggested especially for those patients who meet criteria for possible bvFTD with normal neuroimaging.

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