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Differential Diagnosis of Cognitive Impairment in Bipolar Disorder: A Case Report

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Abstract

In old age bipolar disorder (BD) patients, cognitive complaints difficults an accurate differential diagnosis between cognitive deficits secondary to a primary affective disorder and neurocognitive disorders, such as dementia in Alzheimer's disease (AD). This case report refers to a female 56-year-old patient with severe and treatment resistant BD type I that presented cognitive decline with loss in recent episodic memory and executive functions in the past year. The diagnosis of mild stage dementia associated to BD was suggested, however neuroimaging tests such as magnetic resonance imaging (MRI) and positron emission tomography with fluordeoxiglicose (PET - FDG) were not enough to exclude the differential diagnosis of AD. The CSF biomarkers (reduced levels of amyloid peptide Aβ1-42 and the elevation of total tau protein and phosphorylated tau levels) resources were decisive for exclusion of an etiological diagnosis of AD.

Keywords: Bipolar disorder; Alzheimer's disease; Cognitive impairment; Neuroimaging

Introduction

Bipolar disorder (BD) is a serious and chronic disease that affects the mood regulation and is characterized by alternating episodes of mania or hypomania with depression. The disease is complex with a variable course and psychopathological characteristics that difficult its therapeutic management [1].

The recent episodic memory and learning deficits in BD have been linked to failures in attentional resources, important for memory consolidation, and appear both in acute phases and persist during euthymia [2]. The memory dysfunctions are sensitive to subtle subsyndromal fluctuations, especially the depressive type. Recent publications, in which effects of subsyndromal affective symptoms were controlled, reveal the presence of changes in verbal memory as possible clinical markers trace or cognitive endophenotypes [3,4]. Recent publication demonstrated that both euthymic patients and in maniac episodes presented difficulties to evoke the information required in the California Verbal Learning Test (CVLT) [5]. A previously published meta-analysis found effects of moderate to high intensity of the disease in verbal memory tests and especially in verbal learning and free memory, both short and long term [6].

Currently, it is still not possible to say whether cognitive deficits in BD are prior to the onset of the disease, are the consequence of the disease and its treatment (particularly the polypharmacy) [7] or are a product of their combination. According to some authors, the memory changes depends on clinical status at earlier ages, that over time, become a trait due to neurotoxicity associated with multiple episodes affecting the functioning of the prefrontal and medial temporal cortex [8]. This neurotoxic model suggests that multiple relapses lead, through higher levels of cortisol [9], to neurostructural changes that could be accompanied by cognitive dysfunctions that persist after clinical remission. The patient would recover the episode; however, the microstructural changes would experience a slow or irreversible recovery in some cases 3. The number of maniac episodes is associated with high DNA oxidation in BD type I and this would be one of the potential markers of neuroprogression of the disease [10].

The Alzheimer's disease (AD) is the main cause of dementia in the world, a phenomenon that is also observed in developing countries, as Brazil [11]. Dementia syndromes are characterized by cognitive decline acquired, with progressive course when due to neurodegenerative processes, and that interfere with the individual autonomy to perform the activities of daily living. Almost invariably the cognitive and functional impairment comes with neuropsychiatric issues in the course of the disease. This phenomenon is particularly complicated in the patient who already has a psychiatric illness, with dementia symptoms mixing with the underlying disease [12,13]. During a dementia disorder, the presence of neuropsychiatric issues account for deleterious outcomes, such as accelerated functional decline [14], more effort and emotional distress imposed on caregiver [15], increased risk of patient harm or suffer aggression [16], increased risk of institutionalization [17] and greater morbidity and mortality [18,19].

The distinction of the origin of cognitive impairment in an elderly patient, whether resulting from own BD or concomitant occurrence of AD, or if deleterious result of overlapping both conditions remains an open question. This case report illustrates a common situation in the clinical practice in which patients with longstanding BD (around 30 years of disease, in the present case) and severe episodes of mania and depression, begins to present cognitive complaints. Similar cases challenge the clinician to establish the differential diagnosis between the presence of cognitive impairment secondary to mood disorder or a primary dementia, mainly due to AD.

Case Presentation

Identification and family history

The patient M.N. is a 56-years-old, female, white and divorced, born and living in São Paulo; with 8 years of schooling and is a Catholic. Father with alcohol dependence; mother depressed, obese and hypertensive; sister with epilepsy and brother with severe depression.

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The patient smoked about 1 pack/day since age 18, hypertension diagnosed 10 years ago, and chronic obstructive pulmonary disease diagnosed 5 years ago.

Past psychiatric history

At 18 she presented panic disorder in early postpartum treated with fluoxetine up to 80mg/day for 14 years with a satisfactory response. From 32 to 42 years presented melancholic depression treated with clomipramine up to 150mg/day with periods of improvement and some relapses. After 42 was diagnosed with BD type I after presenting a maniac episode during treatment with clomipramine at a dose of 225mg/day, when then began taking lithium. From 42 to 56 years presented several mood episodes, most depressive with mixed features and 2 episodes of mania associated with paroxetine up to 40mg/day with brief periods of euthymia between phases. She used a lot of combinations of anticonvulsants (valproic acid, lamotrigine and oxcarbazepine) and antipsychotics (trifluoperazine, olanzapine, quetiapine, ziprasidone and aripiprazole). Maintained lithium since the beginning of the BD because of satisfactory response and good tolerance to side effects. Has been hospitalized two times since the diagnosis of BD with non-psychotic major depressive episodes.

Cognitive impairment history

In November 2014 the patient daughter reported that her mother has been showing forgetfulness for a year and causing irritability in family due to the need to repeat events happened. Started to have difficulties to store latest information as newly presented people's names or phone numbers dictated by a family member. At November she was taking lithium 600mg/day, divalproex 750 mg/day, paroxetine 40 mg/day and clonazepam 1mg/day and was euthymic without abusing benzodiazepines. For clinical comorbidities was taking captopril 25 mg/day and simvastatin 20 mg/day and denied the use of other medications or drugs. Physical examination was normal except for central obesity with a body mass index (BMI) of 34.4 kg/m^2.

Investigations

Neuropsychological assessment

The neuropsychological evaluation included CERAD battery (*Consortium to Establish the Registry of Alzheimer's Disease*) consists of five tests: verbal fluency, Boston test, word list memory test (recall and recognition), building praxis and the MMSE [20]. As a complement was included the *Auditory Verbal Learning Test Rey* (RAVLT) [21], *Stroop Color Word Test* [22] and *Trail Making Test* [23]. All the applied tests demonstrated a deficit score. The functionality evaluation using the *Pfeffer Functional Activities Questionnaire* [24] demonstrated functional impairment. Thus, the cognitive and functional screening allowed the hypothesis of a demential syndrome.

Laboratory assessment

Laboratory tests were performed on blood in order to rule out reversible metabolic causes of dementia (blood count, serum sodium, serum potassium, serum calcium and serum phosphorus, serum urea and creatinine, D and B12 vitamins, serum TSH and T4, parathyroid hormone and serological tests for HIV, syphilis, B and C hepatits) did not show alterations.

Structural neuroimaging

The magnetic resonance imaging (MRI) showed increased liquoric spaces suggesting global brain volume reduction with a slight predominance temporal and parietal left and discrete hyperintense foci in T2 and FLAIR in the periventricular white matter usually related to gliosis and microangiopathy (Figure 1).

Functional neuroimaging

Because of the lack of specificity of the morphological findings at MRI, it was decided to evaluate the metabolic activity of the brain neuronal tissue by examining positron emission positrons marked by 18-fluoro-2-deoxy-glucose (FDG-PET). This technique contributes

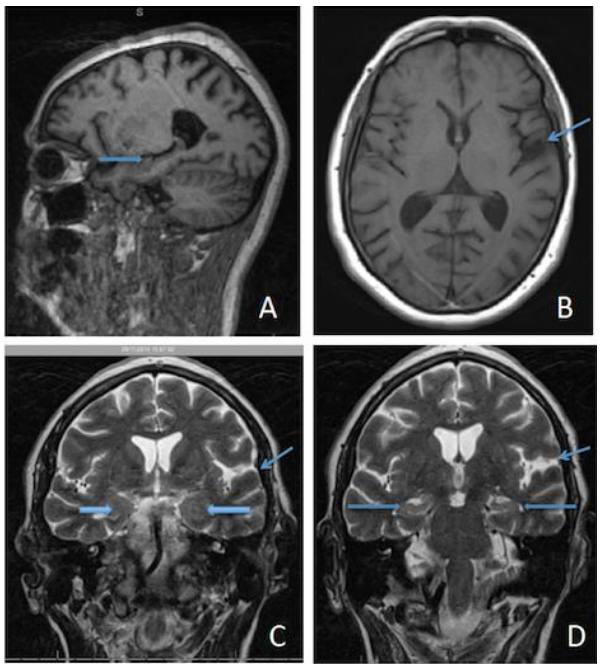

Figure 1: MRI. (A) (Sagittal cut, T1) observed a slight decrease of hippocampal volume (arrow). (B) (Axial cut, T1) slight reduction of the left inferior frontal gyrus (arrow). (C) (Coronal section, T2) normal volume of tonsils (thick arrows) and discreet enlargement of the left lateral groove (thin arrow). (D) (Coronal section, T2) hippocampi with slightly lower volumes (thicker arrows) and discreet enlargement of the left lateral groove (thin arrow).

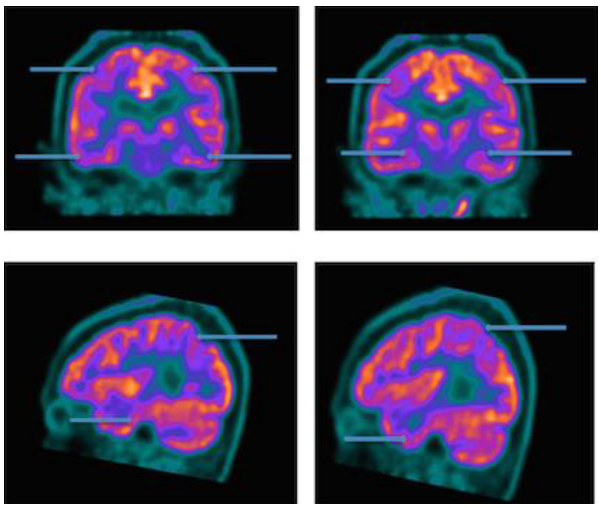

Figure 2: PET-FDG (Coronal and sagittal sections). Hypometabolism in bilateral temporoparietal region (arrows).

to a better diagnostic definition particularly when MRI is doubtful. The picture showed hypometabolism predominantly in bilateral temporoparietal region (Figure 2).

CSF biomarkers assessment

In AD occurs an increased storage of beta - amyloid protein in brain parenchyma. Consequently, there is significant reduction in CSF levels of beta-amyloid protein. In addition, there is increased CSF levels of total Tau and phosphorylated Tau proteins. The results of CSF analysis do not indicate AD: beta-amyloid protein: 1.152pg/mL (normal > 540); total Tau protein: 199 pg/mL (normal < 450 pg/mL) and TAU phosphorylated protein: 47 pg/ml (normal <61 pg/mL).

Discussion

In individuals with long evolution of BD can be difficult to differentiate a cognitive complaint as being secondary to mood disorder from a primary neurocognitive disorder as AD. The patient of this case report is relatively young, but there are several potential factors of poor prognosis, including the age of early onset of psychiatric symptoms; the presence of affected first-degree relatives and course of the disease with severe episodes and hard control disease, leading to exchanges and pharmacological tests combinations at several times. Therefore, it is plausible to assume that the disease, with severe episodes of mania and depression over the years cause cortical insults that contribute to dementia, possibly associated with a neurodegenerative process yet to be clarified 7. However, unlike what is observed in AD, establishing the diagnosis of dementia in BD, with a defined pattern of cognitive and functional decline, remains a major challenge, although attempts have arisen in that direction [25].

The neuropsychological e functional data and medical history, we established the hypothesis of a mild dementia. However, for the differential diagnosis of the etiology of the dementia, it was imperative to conduct imaging and cerebrospinal fluid analyzes. Neuropsychological assessment reveals prominent decline in episodic memory, delayed memory, semantic memory, language, executive functions and attention. The most affected functions were memory and executive functions, respectively associated with mesial temporal lobe regions, especially hippocampus, and frontal regions. The assessment of instrumental functionality also revealed score indicating difficulty in carrying out daily activities characterized by a degree of complexity and a medical history indicated cognitive and functional impairments compatible as mild dementia. As the AD liquoric biomarkers remained within normal limits, and as there is no other determinants of clinical deterioration, it is suggested that dementia is due to BD. The hypothesis that BD per se, is a clinical condition that increases the risk of progression to dementia has been proposed by several studies although little investigated [26-28].

Structural neuroimaging studies point out, as main findings on BD, the bilateral volume reduction of the prefrontal cortex and the anterior cingulate, volumetric enlarged tonsils and hyperintensities outbreaks in subcortical and periventricular regions [29-31]. In the AD, is described a progressive and bilateral reduction of the temporal and parietal lobe volume. In the early stages, there is atrophy of the mesial temporal lobe regions, especially the hippocampus; with the progression of the neurodegenerative process, there is also involvement of other regions, as areas of the frontal cortex [32,33]. In MRI was identified an overall volume reduction with a slight predominance on the left temporal regions, inferior frontal lobe and parietal regions, evidenced by increased Sylvian fissure. Also observed a slight decrease of hippocampal volume, bilaterally, suggesting mild atrophy according to visual scale Duara [34]. The functional neuroimaging (FDG-PET) could contribute to a better definition of brain areas possibly involved in dementia. Moreover, the occurrence of cerebral hypometabolism could precede the observation of structural changes, because the onset of cognitive decline in this patient was recent. AD patients often have hypoperfusion of the temporal and parietal lobes bilaterally, involving the associative cortex in cognitive and functional decline [35]. Changes in brain metabolism associated with clinical deterioration context may be indicative of AD despite the structural abnormalities are not yet evidenced by MRI [36].

In this case report, the results of structural and functional neuroimaging brought ontributions, however, were not enough for definitive clarification of the etiology of dementia. The definitive confirmation as to whether the AD could only be made through the investigation of CSF biomarkers. The finding on the cerebrospinal fluid of reduced beta-amyloid protein and increased total Tau protein, and, phosphorylated Tau protein, strongly indicates a pathophysiological process of AD. However, CSF biomarkers were within normal limits what excludes the hypothesis of AD.

From the neuroplasticity point of view, BD decreases neuronal resiliency and affect the functioning of synapses whose impact can lead to dysfunction and neuronal atrophy and impairment of brain networks interconnect areas [37]. The process of neuroplasticity and neuronal interconnection pathways between the largely cells are regulated by kinase-3β enzyme glycogen synthase (GSK-3β) [38]. Interestingly, the chronic use of lithium for bipolar patients tend to produce a neuroprotective effect. There is a body of evidence that has been increasing in recent years and which gives the lithium the property of inhibiting the unregulated activity of GSK-3β and thereby reduce the risk of hyperphosphorylation of this enzyme [39,40]. The GSK-3β, when activated increases the production of β-amyloid peptide to promote the activity of γ-secretase, which in turn induces aggregation and deposition of β-amyloid protein in brain parenchyma, as well as triggers the hyperphosphorylation of Tau protein [40,41]. This phenomenon contributes decisively to the emergence of AD pathophysiology.

On the other hand, the lithium neuroprotection for the AD suggested by epidemiological studies [42,43] is probably linked to their action to inactivate the GSK-3β and thereby inhibit or attenuate the amyloid cascade and Tau protein phosphorylation. If the chronic use of lithium would have played a neuroprotective role, delaying a possible neurodegenerative process compatible with AD, is an open question. Recent meta-analysis found that the reduction of hippocampal volume in depressed and not found in bipolar patients was due to the use of lithium, which would have masked the degeneration [44]. However, the clinical and cerebrospinal fluid biomarkers, until now, do not suggest the presence of AD in this patient.

Conclusion

We conclude that the cognitive and functional deficits of the patient allow suspect that dementia was strongly associated with BD itself. Finally, the clinical course of dementia in BD associated with the severity of depressive and manic episodes and use over time of drugs not always neuroprotective, represent diagnostic and therapeutic challenges.

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