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Preliminary communication

A case series on the hypothesized connection between dementia and bipolar spectrum disorders: Bipolar type VI?

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Abstract

Background: The concept of bipolar spectrum disorders has opened therapeutic opportunities for patients with atypical and complex affective conditions. The literature has recently described several commonalities in pathophysiological processes of bipolar disorders and dementia. However, this connection has been insufficiently appreciated at the clinical level, in part because affective dysregulation in the elderly and, particularly in the dementia setting, is typically attributed either to secondary depressive states or otherwise relegated to a neurologically understandable behavioral complication resulting from cerebral disease.
Methods: We selected a case series of 10 elderly patients with late-onset mood and related behavioral symptomatology and cognitive decline without past history of clear-cut bipolar disorder. Clinical features, temperament, cognition, family history and pharmacological response were assessed to identify prototypical patients to illustrate the complexities of the dementia–bipolar interface.
Results: Mixed and depressive mood symptoms were most commonly observed and all patients had been premorbidly of hyperthymic, cyclothymic and/or irritable temperaments. Most patients had a family history of bipolar disorder or disorders related to the bipolar diathesis. Symptoms were often refractory to or aggravated by antidepressants and acetylcholinesterase inhibitors, whereas mood stabilizers and/or atypical antipsychotics were beneficial, promoting behavioral improvement in all treated patients and marked cognitive recovery in five.
Limitations: Case series with retrospective methodology.
Conclusion and clinical implications: Patients with cognitive decline and frequent mood lability might be manifesting a late-onset bipolar spectrum disorder, which we posit as type VI. We further posit that dementia and/or other biopsychosocial challenges associated with aging might release latent bipolarity in such individuals. Antidepressants, even drugs targeting dementia, might aggravate the behavioral dysregulation in these patients. Evaluation of premorbid temperament and/or family history of bipolarity and related disorders might help in broadening the clinical and biological understanding of such patients, providing a rationale for better customized treatment along the lines of mood stabilization and avoidance of antidepressants.

Keywords: Dementia; Alzheimer's disease; Mania; Mixed state; Mood stabilizers

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1. Introduction

Bipolar disorders and dementia have been regarded as distinct and unrelated clinical entities. In contrast to unipolar depression, which can conceivably start at any age, bipolar spectrum disorders as a rule have been neglected in the differential diagnosis of dementia. More often than not, affective and related behavioral disturbances in the dementia population are either considered as behavioral complications or attributed to depression and treated with antidepressants. Nevertheless, bipolar disorder may account for as much as 20% of mood conditions in the elderly (Cassano et al., 2000). As for elderly patients with dementia, at least one prospective study has reported that, compared with those with osteoarthritis and diabetes mellitus, there is increased risk of being admitted to a hospital with mania (Nilsson et al., 2002).

Although the first episode of full-blown classic mania in the elderly is rather uncommon, mood instability, mixed irritable–agitated episodes and "atypical" depressions may emerge from the sixth decade of life along with cognitive decline in previously healthy individuals. In an earlier review on this topic, we suggested that the intersection of dementia and bipolarity might give rise to a mixed–labile manic state, which we tentatively suggested to consider as "bipolar type VI" (Akiskal et al., 2005a). A year later, a case report of co-occurring mania and vascular dementia appeared in the literature (Senturk et al., 2006).

We hereby further test the clinical thesis that mixed–labile–agitated episodes in the setting of dementia might represent a putative late-onset bipolar spectrum disorder type VI, beyond the Akiskal and Pinto (1999) framework of type I (mania and depression), type II (cyclothymia and hypomania), type III (depression plus drug-induced hypomania), type IV (late-onset depression superimposed on hyperthymic temperament) and type V (cyclic mixed depressions). In support for such a putative bipolar type VI, we report clinical cases and the theoretical grounds for a yet unappreciated bipolar–dementia connection, focusing on mixed–labile phenomenology, sub-bipolar temperaments, bipolar family history and therapeutic response as preliminary validators.

We present our perspective as an *alternative* to the more commonly held clinical–neurological view that agitation, impulsivity and related mood instability in Alzheimer's and other dementia patients merely represents frontal lobe dysfunction (Senanarong et al., 2004). A more sophisticated view in the literature argues that behavioral–cognitive syndrome in Alzheimer's disease is a prodromal stage, whereas in fronto-temperal dementia the behavioral disorder appears when the cognitive deficit is relatively mild (Jenner et al., 2006). Our perspective, while ostensibly recognizing the dementia setting postulates the possible contribution of pre-existing *familial and/or temperamental diathesis for bipolarity* in patients presenting with dementia-like clinical pictures with marked mood and behavioral disturbances. We thereby hope to go beyond the clinical-descriptive approach (Lyketsos et al., 1995; Leroi et al., 2003).

2. Methods

We present ten patients with cognitive deterioration, mood symptoms in the absence of clear-cut personal history of premorbid bipolar I or II disorders.

The first 5 of these cases were selected from a cohort of elderly Hispanics participating in an adult day treatment program in an underserved area, close to the Mexican border in California. These cases are an accurate reflection of usual mood presentations seen in this Hispanic population attending this adult treatment center. Patients were chosen among those with unmistaken history of agitation, aggression (verbal/physical), increased psychomotor activity and disinhibition in the setting of depression and cognitive dysfunction. Participants in this adult day treatment center receive a baseline semi-structured psychiatric evaluation following DSM-IV TR criteria, a Folstein MMSE (Folstein et al., 1975; Crum et al., 1993) and the Temperament Scale Autoquestionnaire (TEMPS-A). The latter is a psychometrically validated scale of 5 different temperament domains that has shown positive course correlations between the different traits and changes in an individual at risk for mood variations (Akiskal et al., 2005b). As part of the initial evaluation, history for these traits is systematically obtained from family members who have known the patient well before, typically decades, before the onset of the dementing disease. In other words, the temperaments in our case series refer to the premorbid life-long temperament.

The other 5 patients in the present case series are from private clinical practice in Brazil by psychiatrists acquainted with these constructs. These patients were referred from other specialists to treat refractory cases of mood disorders associated with cognitive decline in the elderly. The same diagnostic family history and temperamental conventions were used in this setting.

Approval for conducting retrospective chart review was obtained from the University of California at San Diego Institutional Board for Protection of the Human Subjects. The study was also conducted in line with