abstract

Mania in old age represents a neuropsychiatric syndrome reflecting its neurobiologic basis. This paper reviews the evidence for affective vulnerability (usually genetic) that is associated with the late manifestation of mania often precipitated by neurologic disease. Cerebrovascular pathology is a common comorbidity that is evident clinically or by neuroimaging. Localization of brain lesions to the right side and involving the orbito-frontal circuit appear to be specific to late-onset mania. The implications for management of mania in old age require further systematic evaluation.

Key words: mania, old age, neuropsychiatric syndrome, bipolar disorder, secondary mania

Mania in Old Age: A Neuropsychiatric Syndrome

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Nosology and Classification

Mania is both a symptom and a syndrome, and the term tends to be used rather loosely in the medical literature. It is the essential feature of the psychiatric condition known as bipolar disorder. However, the concept of bipolarity also embraces less severe forms of mania known as hypomania and includes a spectrum of mood disturbances. Bipolar II disorder, for example, encompasses episodes of major depression with milder forms of hypomania. Some researchers also differentiate those whose manic or hypomanic symptoms emerge only after antidepressant treatment from those who exhibit spontaneous episodes.

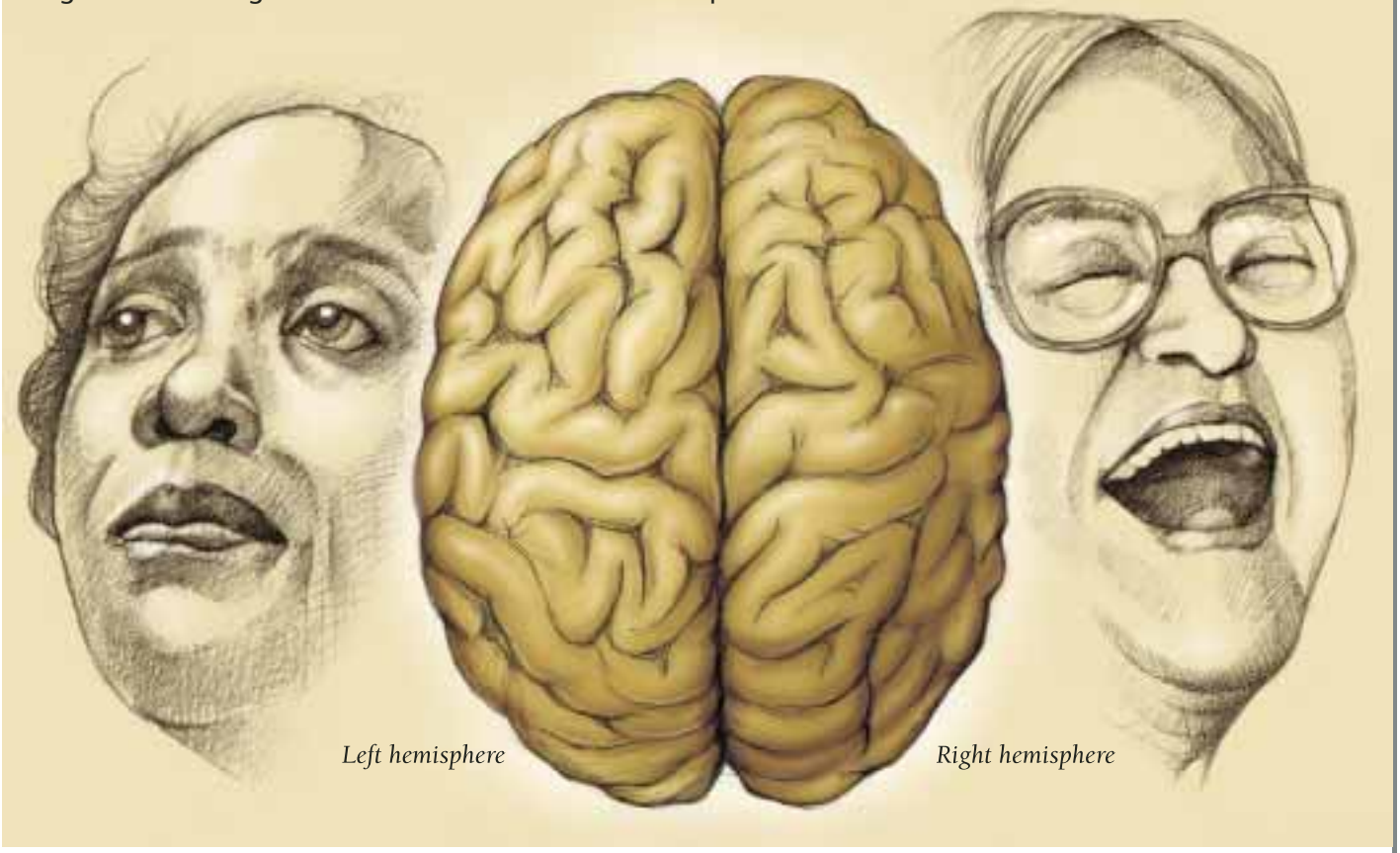
In old age, another diagnostic issue that commonly arises is the notion of secondary mania.[1] Secondary mania was originally described as having no prior history of mood disorder and no family history of psychiatric illness. Moreover, the organic disorder was expected to occur in close temporal proximity to the emergence of mania. This diagnosis implies that the manic syndrome is due to organic factors that are somehow more obvious than those seen in younger, mixed-age bipolar patients. Indeed, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) has established a category of "mood disorder due to a general medical condition" (293.83) with the direction that "the disturbance is the direct physiologic consequence of a general medical condition."[2] However, the high prevalence of medical and neurological disorders in older people makes it difficult to be certain that a psychiatric syndrome such as mania is indeed due to an underlying medical condition. When is the comorbidity of a medical or neurological disorder simply a precipitant and when is it etiological?

In parallel, the neurological literature describes disinhibition syndromes that appear to be identical to the psychiatric concept of mania.[3] The blurred line between neurological disinhibition and psychiatric manic syndromes invites further examination and discussion. In this paper, the data associated with mania in late life will be reviewed and diagnostic subtypes will be revisited. Specifically, the case will be made that mania in late life, especially when it occurs for the first time, is a true neuropsychiatric disorder where the boundaries between neurology and psychiatry are blurred.

Age of Onset

It has been argued that age of onset may be a variable that can distinguish subtypes of mania and lead to an improved understanding of its pathogenesis and etiology.[4] The question of what age can be used as a cut-off for late onset has been debated widely. Wylie *et al.* have suggested that the mean age at onset in a sample of mixed-age patients could be used to establish the cut-off between early and late onset.[5] While there is still debate as to the convention for late-onset mania in an older cohort, the age of 50 would appear to be a reasonable marker. This convention is consistent with empirical findings of age of onset in older bipolars whose index episode is early to mid-70s. Using this approach, Wylie *et al.* demonstrated a significant increase in cerebrovascular risk factors in late- versus early-onset cases.[5] Similarly, an

Figure 1: Pathological Conditions Related to the Hemispheres of the Brain



Cerebral lesions associated with secondary mania and disinhibition syndromes are heterogeneous in nature and tend to affect the right hemisphere. Lesions affecting the right side of the brain produce pathological laughing, while left-sided lesions tend to produce pathological crying.

increase in vascular comorbidity was found in a sample of late-onset older bipolar patients whose mean age was 74 years where age 50 was used as the cut-off for late onset.[6] Rather surprisingly, both early- and late-onset groups showed an extremely high prevalence of positive family history. Despite the caveat that secondary mania is associated with no or low family history of mood disorder, findings have tended towards the opposite conclusion in studies of late-life mania where positive family history in first-degree relatives ranged from 24–88%.[7–11] Still, late-onset patients, especially those with comorbid neurological disorders, tend to have a lower prevalence of family history of mood disorder.[10–12] However, even within the neurological subgroup of patients with secondary mania, a prevalence of positive family history in first-degree relatives as high as 30% has been found.

Twenty percent of first admissions for bipolar disorder in Finland occurred after the age of 60.[13] This finding on hospitalization rates is in stark contrast to community surveys, which tend to find a very early age of onset of about 20 years.[14,15] In studies involving mixed-age manic patients, the mean age of onset tends to be slightly higher at 30 years.[16,17] Given the early onset of bipolarity in a general population, it is worth noting that very few older bipolar inpatients are known to have experienced their first manic episode before the age of 40.[10,11] By contrast, those young early-onset bipolars do not continue to require psychiatric admissions in old age. Whether they burn out over time or have a higher mortality rate because of other non-accidental causes of death remains an interesting question. Indeed, these older late-onset bipolars probably represent a qualitatively different group, with this difference most likely relating to neurologic changes addressed in this discussion. The refrain "where have all the young bipolars gone?" has still not been answered.

Neurologic Comorbidity

One of the most striking findings associated with manic syndromes in late life is the high prevalence of neurologic disorders.[18] Limited studies of mania in old age have consistently found an association with heterogeneous neurological disorders as high as 36% compared to age and sex-matched cases of depression (8%).[11] Within the manic subgroup, if mania was the first affective episode late in life, there was an even greater likelihood that a coarse neurological abnormality was present (71%) compared to older patients with multiple previous episodes of bipolar disorder (28%). Very late onset mania carries a very high neurologic comorbidity and mortality

primarily due to cerebrovascular disease.[12]

The neurology literature refers to disinhibition syndromes and occasionally uses the term secondary mania,[19] whereas the psychiatry literature includes both secondary mania[1] and the broader term of bipolarity. The available evidence tends to be restricted to individual case reports and small case series, but the data is consistent that cerebral lesions associated with secondary mania and disinhibition syndromes are heterogeneous in nature and tend to affect the right hemisphere.[20–22] This is consistent with findings related to pathological laughing and crying, in which lesions affecting the right side of the brain produce pathological laughing, while left-sided lesions tend to produce pathological crying (Figure 1).[23] A Canadian study that reviewed published single case reports of mood disorders associated with focal unilateral cortical lesions also found a trend towards right-sided lesions for manic-like syndromes[24] (see Figure 2). The orbito-frontal circuit (OFC) has been implicated in disinhibition syndromes and secondary mania.[19]

Despite the heterogeneous nature of disorders reported in the literature, the overwhelming prevalence of cerebrovascular disease associated with mania has led to the proposal of a vascular subtype,[22] similar to a proposal of vascular depression.[25] This vascular subtype of mania is defined in the context of cerebrovascular disease based on clinical or neuroimaging findings with further evidence of neuropsychological impairment on formal testing. The clinical evidence includes focal signs, TIAs, or obvious stroke, while findings on neuroimaging include evidence of silent cerebral infarctions or deep white matter hyperintensities. The cognitive or neurological impairment most often associated with these disorders is in memory and executive function, which may explain the disinhibited, socially inappropriate behaviour associated with mania. Further supporting evidence of a vascular subtype would include late onset, a switch from depression to mania in close temporal proximity to the onset of vascular disease, negative family history, and greater impairment of independent activities of daily living.

The cognitive dysfunction associated with mania in late life most likely reflects the underlying cerebrovascular pathology.[22] Whether these patients go on to develop a dementia has not been established, but the findings of Alexopoulos *et al.*[26] in the study of pseudodementia and major depression suggest that long-term follow-up may be necessary to determine whether dementia is indeed a more common outcome of manic syndromes in late life.

The general findings on neuroimaging associated with mania in late life fall into three categories: (1) preponderance of subcortical hyperintensities; (2) decreased cerebral blood flow; and (3) evidence of silent cerebral infarctions.[27,28]

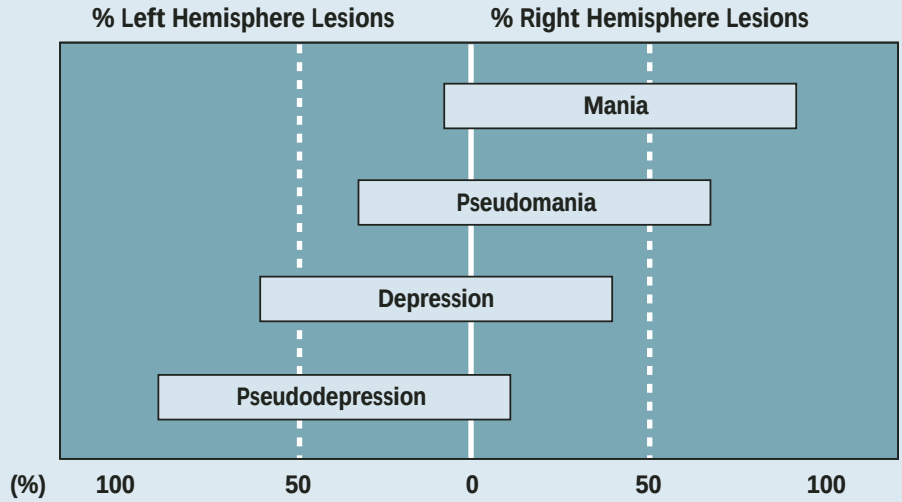
Silent cerebral infarctions were found to occur most commonly in late-onset mania when compared to a group of age-matched depressive patients. Indeed, the proportion of manic patients over the age of 60 who were found to have cerebral infarctions was greater than 20%. These patients were also found to have a relatively modest family history in first-degree relatives.[28] Furthermore, the association of hyperintensities with cardiovascular risk factors such as hypertension, artherosclerotic heart disease, and diabetes mellitus strengthens the relationship of mania to cerebrovascular pathology and supports the notion of a vascular subtype of mania.[22]

Clinical Course and Outcome of Mania in Late Life

In a cohort of hospitalized older bipolar patients, half the patients had their first episode as a major depression.[11] Within this group of first episode depressives, a mean latency of almost 15 years preceded the onset of the first manic episode.[11,29] Over half of such older patients with bipolar disorder had at least three distinct depressions within that latency period before mania became manifest.[8,10,29] The apparent "conversion" to a bipolar diagnosis after many years of a unipolar course is associated with comorbid neurologic disorders.

There is limited data on long-term clinical outcomes in older bipolar patients.[11,30,31] In two of the studies with a mean six-year follow-up, a high mortality was reported. In one study, 50% of the older manic patients had died at six-year follow-up compared to only one-fifth of age- and sex-matched older depressives. Others have shown a significant decline in cognition of older bipolars.[30,31] In short, aged manic patients

Figure 2: Focal Unilateral Cortical Lesions



Source: Braun CM, *et al.*[24]; used with permission.

experienced high rates of mortality and morbidity at outcomes reflecting the underlying central nervous system pathology and neurologic comorbidity associated with these syndromes.

Mania as a Neuropsychiatric Disorder

Affective Vulnerability

Notwithstanding the general pattern of a lower genetic loading in late-onset bipolar cases and in patients who had neurologic disorders, there is still an affective predisposition with significant familial prevalence of mood disorder in first-degree relatives of older bipolars.[6,11] In addition, clinical experience suggests that this affective vulnerability is not restricted solely to genetics but may potentially relate to early psychological trauma, which may include the loss of a parent or childhood abuse. However, this requires further investigation.

Multifactorial Elements

The late conversion of unipolar depressives to bipolarity may reflect normal degenerative changes associated with the aging brain or may be associated with more obvious heterogeneous brain pathology as documented by the multiple case reports involving the orbitofrontal circuit and the right hemisphere. Indeed, it appears that the location of lesions is critical to the manifestation of mania in those with an affective predisposition. Common neurologic disorders rarely produce mania in late life. It is this confluence of factors (affective predisposition with specific neurologic damage) that appears to be most relevant to the manifestation of manic syndromes in late life. This highlights the need for psychiatry and neurology to come together to better understand such disorders and ultimately to improve their management.

Conclusion

Mania in late life represents a paradigm for neuropsychiatric disorders. These disorders suggest the possibility of a future clinical neurosciences network that integrates psychiatry, neurology, and geriatric medicine into a more cohesive knowledge base and clinical service. The blurring of boundaries between disciplines involved in the care of older people invites a fresh approach to post-graduate training and the organization of services. Integration of the understanding of brain and CNS function with the understanding of affective, behavioural, and cognitive symptoms is essential. u

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