Psychological Medicine, 2002, **32**, 359–362. © 2002 Cambridge University Press
DOI: 10.1017/S0033291701004718 Printed in the United Kingdom

BRIEF COMMUNICATION

Vascular risk factors in late onset mania

FREDERICK CASSIDY[1] AND BERNARD J. CARROLL

From the Duke-Umstead Bipolar Disorders Program, Duke University Medical Center, Durham, NC, USA

ABSTRACT

Background. Previous researches have suggested that late onset mania is a distinct subtype associated with medical and neurological disorders. Few studies, however, have focused on vascular risk factors.

Methods. Records of 366 bipolar patients were reviewed and age of first psychiatric hospitalization determined. Late-onset cases were determined empirically from a distribution histogram. Late onset cases were matched to early onset cases and histories of vascular disease/risks and current cholesterol levels compared.

Results. The distribution of age of first psychiatric hospitalization was bimodal with an intermode at age 47. Using that threshold, 6·3% of the cohort was classified as having late onset mania. Vascular risks factors were greater and current cholesterol levels higher in the late onset group.

Conclusions. Late onset mania is associated with greater vascular risk factors. The bimodal appearance of age of first psychiatric hospitalization in this study provides further support of late onset mania as a distinct manic subtype with possibly a different, vascular aetiology. Control of these vascular risks may impact on the incidence of late onset mania, as well as on its clinical management.

INTRODUCTION

Cases of late onset mania (LOM) comprise up to 10% of all bipolar disorder (Clayton, 1983). They are less likely to have positive family histories of affective disorders and more likely to have concurrent medical and neurological disorders than cases of early onset mania (EOM, Goodwin & Jamison, 1990).

Few studies of LOM, however, have focused specifically on vascular risks, despite growing recognition of the importance of vascular-based late onset depression (LOD, Fujikawa *et al.* 1993; Krishnan *et al.* 1997). Hays *et al.* (1998) reported greater vascular co-morbidity in six LOM subjects than 68 EOM subjects, but did not control for current age of the groups, limiting the findings. Wylie *et al.* (1999) also compared clinical histories of EOM and LOM patients within an age-restricted cohort of patients 60 years of age or older. Subjects were divided into two groups using an arbitrary age of onset-based median split. The older onset group had more vascular risk factors.

White-matter hyperintensities on MRI scans are more common in subjects with LOD (Fujikawa *et al.* 1993; Krishnan *et al.* 1997) and may be important to the development of LOM as well. McDonald *et al.* (1991) reported increased MRI-detected cerebrovascular lesions in LOM subjects compared with age-matched normal controls. Comparisons with age-matched EOM controls were not undertaken in that study however. Similar MRI findings have also been noted in younger bipolar patients (e.g. Dupont *et al.* 1990; Swayze *et al.* 1990), which limits the findings of McDonald *et al.* (1991).

[1] Address for correspondence: Dr F. Cassidy, Duke-Umstead Bipolar Disorders Program, Box 3414, Duke University Medical Center, Durham, North Carolina 27710, USA.

Fujikawa *et al.* (1995) reported increased rates of cerebrovascular lesions in 20 LOM subjects using a control group that included 10 age- and sex-matched EOM patients in addition to 10 non-bipolar affective disorder patients.

Several studies have indicated a bimodal distribution of age of onset for manic-depression, consistent with the view that LOM may represent a distinct manic subtype (Petterson, 1977; Angst, 1978; Goodwin & Jamison, 1984; Broadhead & Jacoby, 1990). Others, however, have not confirmed a bimodal distribution (Wertham, 1929; D'Elia & Perris, 1969; Spicer *et al.* 1973; Loranger & Levine, 1978; Baron *et al.* 1983; Joyce, 1984; Eagles & Whalley, 1985). Sibisi (1990) also did not confirm a bimodal age distribution of first admissions for mania in a large sample, but did demonstrate a bimodal appearance at least in males when rates in different age groups were adjusted for the corresponding population rates. Of larger studies that included 100 subjects or more, only two reported bimodal distributions of age of onset or population-based incidence (Goodwin & Jamison, 1984; Sibisi, 1990) while another seven did not (Wertham, 1929; D'Elia & Perris, 1969; Spicer *et al.* 1973, Loranger & Levine, 1978; Baron *et al.* 1983; Joyce, 1984; Eagles & Whaley, 1985). Hence, no clear consensus developed. In the current report we examine these issues, analysing histories of a sample of 366 bipolar subjects. Constructing an age-based distribution histogram, we examine whether a distinct late-onset group can be identified and if so whether vascular risk factors are more prevalent in that group.

METHOD

Records of 417 bipolar subjects consecutively evaluated by the Duke-Umstead Bipolar Disorders Program between July 1992 and September 1999 were reviewed. All subjects were hospitalized at John Umstead Hospital (JUH) for the treatment of manic or mixed states of bipolar disorder and met DSM-III-R criteria for bipolar disorder, manic or mixed. Age of first psychiatric hospitalization was available in 366 subjects. A distribution histogram of age of first psychiatric hospitalization was constructed. A bimodal distribution was noted and cases were categorized as LOM or EOM based on that distribution. Sex, race and subtype (manic or mixed) of the two resulting groups were compared using chi-square statistics. LOM cases were matched by sex, race and current age to within 3 years with EOM cases. Histories were reviewed for vascular risk factors/disease comprising hypertension (HTN), cerebrovascular accidents (CVA), coronary artery disease (CAD), atrial fibrillation (AF), diabetes mellitus (DM), and either current fasting cholesterol level of 200 mg/dl or greater or previously diagnosed hyperlipidaemia (HL) and history of smoking (SMK). Fasting cholesterol levels were determined as part of the routine laboratory assessments done on all adult admissions to JUH. Total number of risk factors was computed and matched pairs of EOM and LOM were compared on this total score using the Wilcoxon signed rank test. Fasting cholesterol levels were also compared using paired t tests.

RESULTS

The study cohort

The cohort included 181 males and 185 females. Two hundred and seventeen were white, 147 were African American and one each was Native American and Asian American. Fifty-one met DSM-III-R criteria for bipolar disorder, mixed, and 315 met criteria for bipolar disorder, manic. The mean age of the group was 40·9 years (S.D. 13·4, range 18–82).

Age of first psychiatric hospitalization

The age of first psychiatric hospitalization was not normally distributed (Kolmogorov–Smirnov statistic $P < 0{\cdot}001$). The distribution histogram (Fig. 1) indicates a bimodal distribution with an intermode at age 47. Based on this histogram we defined LOM cases by a first psychiatric hospitalization at age 47 or greater. The remainder were classified as EOM. Twenty-three (6·3%) were classified as LOM and 343 (93·7%) as EOM. As expected, the age of the LOM group (62·6 years, S.D. 10·0) and the EOM (39·4 years, S.D. 12·3) differed ($t = 8{\cdot}870$, df = 364, $P < 0{\cdot}001$). The LOM group included eight African Americans and 15 whites. Eleven were male and 12 were female. Twenty-one met DSM-III-R criteria for bipolar disorder, manic, and two bipolar disorder, mixed. The EOM group included 139 African Americans, 202 whites, one American Indian and one Asian American.

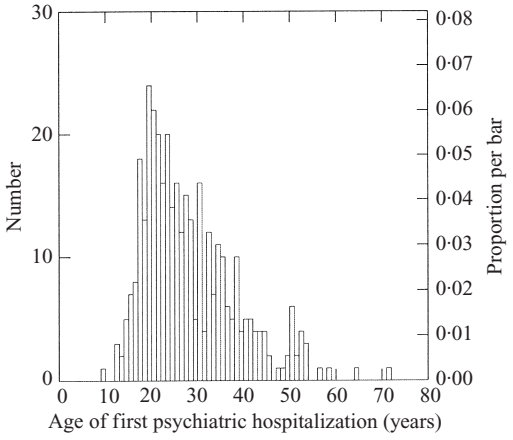

FIG. 1. Distribution histogram of age of first psychiatric hospitalization in bipolar manic and mixed subjects.

Table 1. *Vascular risks/diseases in the early onset mania* (*EOM*) *and late onset mania* (*LOM*) *groups*

LOM	Vascular risks/Diseases	EOM	Vascular risks/Diseases
1	HTN, HL	1	SMK
2	HL, SMK	2	None
3	HTN, HL, CVA	3	HL, SMK
4	HTN, HL, SMK	4	HTN, SMK
5	HTN, SMK, CVA	5	SMK
6	SMK, CAD	6	HTN, CAD
7	None	7	SMK
8	HTN, DM, HL, CAD	8	HTN, DM, HL
9	HL, DM, SMK	9	HTN, HL, SMK
10	DM, HL, SMK	10	HL
11	HL, SMK	11	SMK
12	HTN, HL, SMK	12	SMK
13	DM, AF	13	DM, SMK
14	HTN, SMK	14	HTN, SMK, CAD
15	HL, AF, SMK	15	HTN, SMK
16	HTN, HL	16	HL, SMK
17	HTN, HL	17	HTN, SMK
18	SMK	18	HL, SMK

One hundred and seventy were male and 173 were female. Two hundred and ninety-four met DSM-III-R criteria for bipolar disorder, manic and 49 for bipolar disorder, mixed. Sex ($\chi^2 = 0{\cdot}026$, df = 1, NS), race (white *v.* black, $\chi^2 = 0{\cdot}320$, df = 1, NS) and manic *v.* mixed subtype at time of evaluation (Yates' corrected $\chi^2 = 0{\cdot}192$, df = 1, NS) did not differ between the LOM and EOM groups.

Eighteen of the 23 LOM patients were matched by sex, race and age to within 3 years with EOM patients and vascular risk factors/disease were reviewed. Five LOM patients (two African American males age 57 and 71, two African American females age 77 and 78, and one white male age 82) could not be matched within the established parameters and were not included in these analyses. All five had histories of at least one vascular risk factor (1 HTN; 1 HTN and CAD; 1 CAD and SMK; 1 HTN, DM and HL; and 1 HTN, DM, HL, SMK). Vascular risks/diseases of the remaining 18 are listed in Table 1. Of these, 16 had two or more vascular risks/diseases and eight had three or more (Table 2). Of the 18 matched controls, 11 had two or more vascular risks/diseases and only three had three or more. Fasting cholesterol levels in the 18 LOM patients (210·7, S.D. 42·4) and in the age-matched early-onset manic patients (176·2, S.D. 38·7) were significantly different ($t = 3{\cdot}200$, df = 17, $P = 0{\cdot}005$). None of the subjects had been treated with cholesterol lowering medications at the time of cholesterol determination. One patient in the LOM group had been treated with an atypical antipsychotic medication prior to sample collection. The LOM group had more vascular risk factors/vascular disease (Wilcoxon signed rank test $Z = -2{\cdot}221$, $P = 0{\cdot}026$). The mean ages of the LOM group (59·0 years, S.D. 8·3) and the matched EOM group (58·6 years, S.D. 8·4) did not differ ($t = 0{\cdot}984$, df = 17).

Table 2. *Number of matched patients with* 0–4 *vascular risks/diseases grouped by late* v. *early onset. No patient had* > 4 *vascular risks/diseases*

Number of vascular risks	LOM *N*	EOM *N*
0	1	1
1	1	6
2	8	8
3	7	3
4	1	0

DISCUSSION

Our data revealed a distinct subgroup of late-onset bipolar patients, defined by an age of first psychiatric hospitalization of 47 years or greater (Fig. 1), which also generally corresponds with the frequently reported threshold of 50 years for the diagnosis of LOD (Krishnan *et al.* 1995) and is compatible with those larger studies reporting a bimodal age of onset distribution of manic

patients with intermodes in the 5th and 6th decades of life (Goodwin & Jamison, 1984; Sibisi, 1990). Twenty-three of the 366 (6·3%) cases were categorized as LOM, somewhat lower than the 10% noted by Clayton (1983). Retrospectively dating the onset of a disorder may be difficult. In the current report we used the age of first psychiatric hospitalization in an exclusively in-patient sample. Although hospitalization is not required for the diagnosis of a manic episode and bipolar disorder, the functional impairment associated with mania typically results in psychiatric hospitalization.

Twenty-two of the 23 LOM patients had some vascular risk. Vascular risks/disease in the matched LOM group included: SMK, 11 (69%); HTN, 9 (50%); DM, 4 (22%); CAD, 2 (11%); and, a history of AF, 2 (11%). Vascular risk/disease in the EOM group included: SMK, 14 (78%); HTN, 7 (39%); DM, 2 (11%); and, CAD 2 (11%). None of this group had a history of AF. Twelve of the 18 (67%) LOM subjects had fasting cholesterol levels of $\geqslant 200$ mg/dl, whereas 6 of the 18 (33%) EOM subjects had fasting cholesterol levels of $\geqslant 200$ mg/dl.

Our study comprised patients hospitalized at a state psychiatric hospital meeting criteria for bipolar disorder. The relationship of these findings to patients in primarily medical settings who have been diagnosed with organic mood syndromes (e.g. manic mood symptoms related to multiple sclerosis) is unclear and the validity of the nosological separation of these disorders from LOM remains to be established. Based on the current and previous studies, we propose a history of an initial bipolar manic or mixed episode, as defined by DSM-IV, that occurs after the age of 45 as a working definition for late onset bipolar disorder.

Although LOM subjects did demonstrate increased current vascular risk factors/disease, compared with matched EOM subjects, the temporal relationship of these risks to the diagnosis of mania is not known. These vascular risks may play an aetiological role in the development of LOM, as has been suggested for LOD. If so, recognition and control of these vascular risks may impact on the incidence of LOM, as well as on its clinical management.

Funded in part by a NARSAD Young Investigator Award.

REFERENCES

Angst, J. (1978). The course of affective disorders: II. Typology of bipolar manic-depressive illness. *Archiv für Psychiatrie und Nervenkrankenheit* **226**, 57–64.

Baron, M., Risch, N. & Mendlewicz, J. (1983). Age at onset in bipolar-related major affective illness: clinical and genetic implications. *Journal of Psychiatric Research* **17**, 5–18.

Broadhead, J. & Jacoby, R. (1990). Mania in old age: a first prospective study. *International Journal of Geriatric Psychiatry* **5**, 215–222.

Clayton, P. J. (1983). The prevalence and course of the affective disorders. In *The Affective Disorders* (ed. J. M. Davis and J. W. Maas), pp. 93–201. American Psychiatric Association Press: Washington, DC.

D'Elia, G. & Perris, C. (1969). Selbstmordversuche im Laufe unipolarer und bipolarer Depressionen. *Archiv für Psychiatrie und Nervenkrankenheit* **212**, 339–356.

Dupont, R. M., Jernigan, T. L. & Butters, N. (1990). Subcortical abnormalities detected in bipolar affective disorder using magnetic resonance imaging. *Archive of General Psychiatry* **47**, 55–59.

Eagles, J. M. & Whalley, L. J. (1985). Ageing and affective disorders: the age at first onset of affective disorders in Scotland, 1969–1978. *British Journal of Psychiatry* **147**, 55–59.

Fujikawa, T., Yamawaki, S. & Touhouda, Y. (1993). Incidence of silent cerebral infarction in patients with major depression. *Stroke* **24**, 1631–1634.

Fujikawa, T., Yamawaki, S. & Touhouda, Y. (1995). Silent cerebral infarctions in patients with late-onset mania. *Stroke* **26**, 946–949.

Goodwin, F. K. & Jamison, K. R. (1984). The natural course of manic depressive illness. In *Neurobiology of Mood Disorders* (ed. R. M. Post and J. C. Ballenger), pp. 20–37. Williams & Wilkins: Baltimore.

Goodwin, F. K. & Jamison, K. R. (1990). *Manic Depressive Illness*. Oxford University Press: Oxford.

Hays, J. C., Krishnan, K. R. R., George, L. K. & Blazer, D. G. (1998). Age of first onset of bipolar disorder: Demographic, family history, and psychosocial correlates. *Depression and Anxiety* **7**, 76–82.

Krishnan, K. R. R., Hays, J. C. & Blazer, D. G. (1997). MRI-defined vascular depression. *American Journal of Psychiatry* **154**, 497–501.

Loranger, A. W. & Levine, P. M. (1978). Age of onset of bipolar affective illness. *Archives of General Psychiatry* **35**, 1345–1348.

Joyce, P. R. (1984). Age of onset in bipolar disorder and misdiagnosis as schizophrenia. *Psychological Medicine* **14**, 145–149.

McDonald, W. M., Krishnan, K. R. R., Doraiswamy, P. M. & Blazer, D. G. (1991). Occurrence of subcortical hyperintensities in elderly subjects with mania. *Psychiatry Research: Neuroimaging* **40**, 211–220.

Petterson, U. (1977). Manic-depressive illness. *Acta Psychiatrica Scandinavica* **269**, 1–93.

Sibisi, C. D. T. (1990). Sex differences in the age of onset of bipolar affective illness. *British Journal of Psychiatry* **156**, 842–845.

Spicer, C. C., Hare, E. H. & Slater, E. (1973). Neurotic and psychotic forms of depressive illness: evidence from age-incidence in a national sample. *British Journal of Psychiatry* **23**, 535–541.

Swayze, V. W. II, Andreasen, N. C., Alliger, R. J., Ehrhardt, J. C. & Yuh, W. T. C. (1990). Structural brain abnormalities in bipolar affective disorder: Ventricular enlargement and focal signal hyperintesities. *Archives of General Psychiatry* **47**, 1054–1059.

Wertham, F. I. (1929). A group of benign psychoses: prolonged manic excitements. *American Journal of Psychiatry* **9**, 17–78.

Wylie, M. E., Mulsant, B. H., Pollock, B. G., Sweet, R. A., Zubenko, G. S., Begley, A. E., Gregor, M., Frank, E., Reynolds, C. F. & Kupfer, D. J. (1999). Age of onset in geriatric bipolar disorder: Effects on clinical presentation and treatment outcomes in an inpatient sample. *American Journal of Geriatric Psychiatry* **7**, 77–83.