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Journal of Affective Disorders 58 (2000) 215–221

JOURNAL OF
**AFFECTIVE
DISORDERS**

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Brief report

Early and late onset bipolar disorders: two different forms of manic-depressive illness?

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Received 18 June 1998; received in revised form 21 May 1999; accepted 3 June 1999

Abstract

Background: Conflicting results in genetic studies of bipolar disorders may be due to the clinical and genetic heterogeneity of the disease. Age at onset of bipolar disorders may be a key indicator for identifying more homogeneous clinical subtypes. We tested whether early onset and late onset bipolar illness represent two different forms of bipolar illness in terms of clinical features, comorbidity and familial risk. **Methods:** Among a consecutively recruited sample of 210 bipolar patients, we compared early onset ($n = 58$) and late onset ($n = 39$) bipolar patients; the cut-off points were age at onset before 18 years and after 40 years for the two subgroups. The subgroups were compared by independent t tests and a contingency table by raw chi-square test. Morbid risk among first-degree relatives was measured by the survival analysis method. **Results:** The early onset group had the most severe form of bipolar disorder with more psychotic features ($P = 0.03$), more mixed episodes ($P = 0.01$), greater comorbidity with panic disorder ($P = 0.01$) and poorer prophylactic lithium response ($P = 0.04$). First degree relatives of early onset patients also had a higher risk of affective disorders ($P = 0.0002$), and exhibit the more severe phenotype, i.e bipolar disorder. **Conclusion:** Our data suggest that early and late onset bipolar disorders differ in clinical expression and familial risk and may therefore be considered to be different subforms of manic-depressive illness. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Manic-depressive illness; Age at onset; Clinical subtypes; Survival analysis; Familial risk

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PII: S0165-0327(99)00111-1

1. Introduction

Initial enthusiasm for the genetic investigation of affective disorders has recently been tempered by a series of failures to replicate linkage results (Risch and Merikangas, 1996). Conflicting results may be due to the lack of consensus regarding the proper definition of the affected phenotype and the questionable homogeneity of bipolar illness. Thus, attention is shifting towards the study of specific clinical indicators of affective disorders which are familial and may be useful for identifying heritable forms of the illness (Leboyer et al., 1998a). As correlation for age at onset (AAO) has recently been demonstrated between bipolar sib pairs (Leboyer et al., 1998b), AAO could be such an indicator. The clinical characterisation of the subgroups of AAO is of major importance for future studies aiming at the identification of familial vulnerability factors. Lastly, AAO is also implicated in genetic anticipation (this phenomenon refers to the increase in disease severity and decrease in AAO in succeeding generations) which has been suggested in bipolar disorders (Lindblad et al., 1995).

It has been suggested that relatives of early onset bipolar probands have a higher risk of affective disorders than those of late-onset probands (Strober, 1992). Several studies have shown that there are clinical differences between early and late onset bipolar disorders: Early onset bipolar patients have more psychotic symptoms (McGlashan, 1988), more manic episodes (Angst, 1987), and have higher levels of comorbidity with conduct disorders, alcohol abuse, drug addiction and eating disorders (Bashir et al., 1987). They also respond poorly to lithium (Strober et al., 1988). However, several of these findings have not been consistently replicated in other studies. In particular, the higher proportion of manic episodes in early onset bipolar probands was not shown by Taylor and Abrams (1981), and Roy-Byrne et al. (1985), and the poor prophylactic response to lithium in early onset bipolars was not reported by Prien et al. (1974) and Dunner et al. (1976).

These discrepancies may be due to methodological differences. Inclusion criteria are not always consistent and heterogeneous samples have sometimes been studied. The AAO cut-off is usually arbitrarily

chosen and not based on the onset distribution observed in a systematically recruited sample of bipolar patients. In addition, a single age cut-off point is usually chosen to define early and late-onset subtypes (Taylor and Abrams, 1981; Goetzl et al., 1974; Angst et al., 1980) which may mask differences between two groups close to one another. Furthermore, some studies have included only one sample of early or late subjects and have used previously published data to make comparisons (Kutcher and Marton, 1991).

Thus, we undertook a systematic recruitment of Bipolar 1 and 2 patients using standardized instruments to further characterize homogeneous bipolar subgroups. Based on the AAO distribution in our sample, we defined early onset for bipolar disorders as onset before the age of 18 and late onset as onset after the age of 40 years (Fig. 1). We compared these two subgroups on the basis of clinical and familial data.

2. Patients and methods

2.1. Patients and procedures

A sample of 210 bipolar patients was recruited from consecutive admissions to psychiatric units at the Pitié-Salpêtrière (Paris) and Robert Debré Hospitals (Paris). Patients were interviewed using a French version of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). DSM IV and RDC diagnosis were assessed with this questionnaire. We used « diagnostic age » as definition of AAO (i.e. the age at which the patient first met DSM IV criteria for a major depressive episode, mania or hypomania according to medical case notes and interviews). This definition is close to the exact beginning of the illness and is known to be highly reliable ($r = 0.89$ in Egeland et al., 1987).

Lithium response was also recorded during the interview and patients were classified into two groups: non-responders (0) and responders (1) (i.e. relapse when lithium was stopped after at least one year of treatment or no relapse after three years of treatment) (Kennedy, 1993).

Familial psychiatric morbidity was investigated using the Family Interview for Genetics Studies

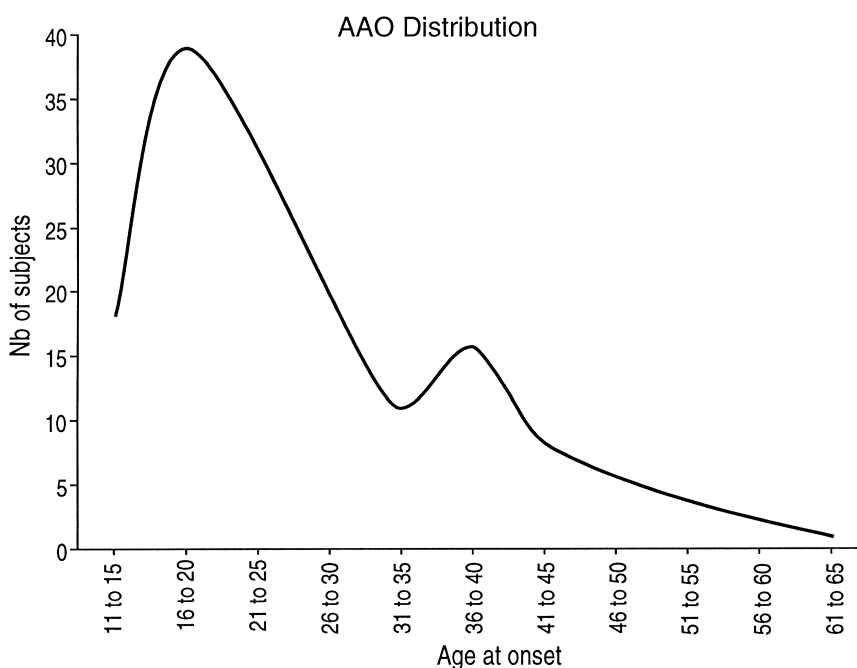


Fig. 1. Distribution of AAO.

(FIGS), (Maxwell, 1992). A complete family history of first degree relatives was obtained from each proband and at least one first degree relative. The information was supplemented if required with medical case notes of relatives.

After complete description of the study to the subjects (proband and relatives), written informed consent was obtained.

2.2. Statistical analysis

Differences in sociodemographic and clinical variables among early and late onset bipolar probands were analyzed by independent *t* tests and a contingency table by raw chi-square tests when appropriate.

We investigated the morbid risk among first degree relatives by calculating unadjusted rates of mood disorders (including major depressive episode, unipolar and bipolar illness) in first degree relatives for early and late onset bipolar probands. The Cox proportional model (Cox, 1972) was used to compare the prevalence of psychopathology among first degree relatives of early and late onset probands. For

the relatives, psychopathology used was presence of unipolar, bipolar illness and single major depressive episode.

3. Results

3.1. Description of the sample

In the whole sample of 210 bipolar patients, we observed two patterns of AAO (Fig. 1). We defined early-onset patients as subjects with a disease onset before the age of 18 years, and late-onset as onset over the age of 40 years. Among our entire sample of bipolar patients, 58 had an early-onset and 39 a late-onset (Table 1). Familial psychiatric morbidity was investigated with FIGS in a subsample of 52 bipolars (32 early and 20 late onset probands). A sample of 254 relatives (102 parents, 109 siblings, 43 offspring) were assessed (Table 2). The remaining 45 families could not be included because FIGS data was not available. The sample of 52 bipolar patients did not differ from the entire set of patients

Table 1
Description of the sample of bipolar patients

	Early onset < 18 years	Late onset > 40 years
Number of probands	58	39
Age at the time of the assessment (years)	33.6±11.9	60.2±9.2
Diagnostic age (years)	15.5±1.9	48.5±7
Age at first treatment (years)	21.8±7.6	49.3±7.4
Age at first hospitalization (years)	24.9±10.2	52.6±8.6

Table 2
Description of the sample of first-degree relatives

	Relatives			
	Parents	Siblings	Offspring	
Early onset probands	64 (32M/32F)	58(25M/33F)	16(10M/6F)	138
Late onset probands	38(19M/19F)	51(28M/23F)	27(11M/16F)	116
	102	109	43	254

M = male.
F = female.

in gender, age at onset, ratio of BP1 and BP2 and number of episodes.

3.2. Clinical data

Clinical comparison of early ($N = 58$) and late ($N = 39$) onset bipolar patients showed no significant difference in sex ratio, bipolar illness type I and type II, number of affective episodes by year, type of first episode (manic or depressive episode), alcohol abuse, suicide attempts. By contrast, early onset probands experienced more psychotic features (delusions and/or hallucinations) during affective episode ($P = 0.03$), and had more mixed episodes ($P = 0.01$) than late-onset probands (Table 3). Concerning lithium response, early onset patients were more frequently “non responders” than late onset patients ($P = 0.04$). Analysis of comorbidity showed that early-onset patients more often had panic disorder ($P = 0.01$).

3.3. Family data

Morbid risk of first degree relatives of early or late onset bipolar probands for major affective disorders are given in Table 4. The morbid risk of first degree relatives for all affective disorders was greater for early onset than for late onset probands ($P = 0.0002$)

(Fig. 2), primarily due to higher levels of bipolar illness ($P = 0.01$). There was no significant difference between groups for the risk of unipolar depression ($P = 0.25$) and major depressive episode ($P = 0.06$) in first degree relatives. The two samples of relatives of early and late onset bipolar patients did not differ in sex ratio and closeness of relationship (parents, siblings, offspring). Stratifications according to proband or relative's gender, the type of bipolarity of the proband (i.e. BP1 or BP2) did not affect the morbid risk.

4. Discussion

The early onset group is characterized by the most severe form of bipolar disorder and appeared to be associated with higher risk of affective disorders among first degree relatives.

As shown in previous studies (for review, see Goodwin and Jamison, 1990), we observed that patients with early onset are more frequently Bipolar I (71%) than are patients with late onset (51%). Early onset probands had more psychotic features, as previously reported (McGlashan, 1988). The higher proportion of mixed episodes in early onset probands may also reflect the greater severity of the disease.

Table 3
Clinical variables and comorbidity diagnosis for early and late onset probands

	Early	Late	P
No. of probands	58	39	
Proportion of males	37.9%	48.7%	NS
BP1 ratio	70.7%	56.4%	NS
Polarity of the first episode (percent of EDM)	79.3%	69.2%	NS
Presence of mixed episodes	30.2%	6%	0.009*
No. of mania/duration of the illness (No of mania/year; Mean±variance)	0.25±0.05/year	0.23±0.07/year	NS
No. of EDM/duration of the illness (No. of EDM/year; Mean±variance)	0.33±0.06/year	0.45±0.31/year	NS
Psychotic features	47.3%	25.6%	0.03*
Panic disorder	21%	2.6%	0.01*
Agoraphobia	7%	0%	NS
Social phobia	10.5%	12.8%	NS
Obsessive compulsive disorder	10.5%	7.7%	NS
Lithium response	43.3%	64%	0.04*
Alcohol abuse or dependence	21%	20.5%	NS
Suicide attempts	41.3%	28.9%	NS
Violent suicide attempts	5.1%	10.5%	NS

Table 4
Prevalence of psychopathology in first-degree relatives

	First-degree relatives			
	EDM	UP	BP1	BP2
Probands				
Early onset	14 (10.1%)	6 (4.3%)	13 (9.4%)	2 (1.4%)
Late onset	7 (6%)	2 (1.7%)	5 (4.3%)	0

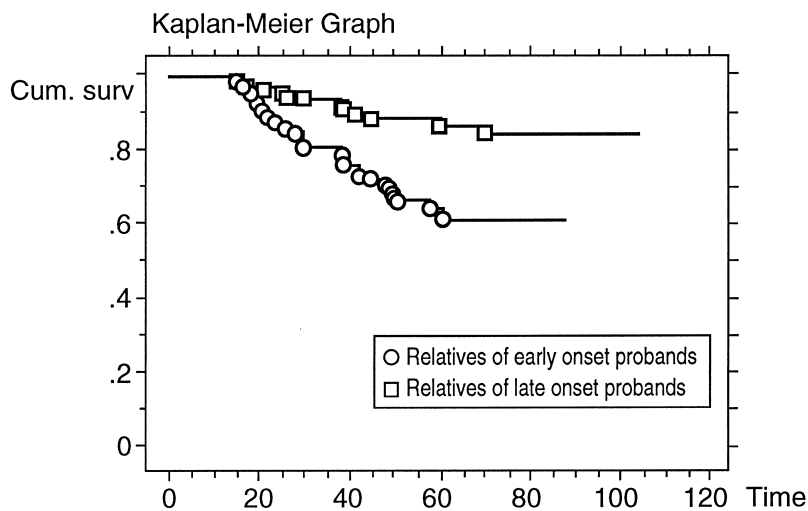


Fig. 2. Morbid risk in relatives according to the proband's AAO.

Early onset patients had a poorer lithium response than late onset, this result was controversial (Grof et al., 1994; Engstrom et al., 1997). These discrepancies might be due to methodological differences such as criteria to assess family history or lithium response. Poor lithium response may reflect the severity of bipolar illness in early-onset patients.

The comorbidity with panic disorder may be a marker of genetic heterogeneity in bipolar disorder as suggested elsewhere (McKinnon et al., 1997). Our data showing that only early-onset bipolar probands have high comorbidity with panic disorder further suggests that this comorbidity may help to identify a subtype of bipolar patients.

Early age at onset was associated with an increased morbid risk for affective disorder among first degree relatives. In addition, we found that the higher risk in relatives of early onset probands is essentially due to higher levels of bipolar disorders by comparison with first degree relatives of late onset probands. Thus, first degree relatives of early onset patients have both an increased morbid risk, and have also inherited the most severe phenotype. This suggests that early and late onset are underlined by different familial loading, early onset bipolar probands being at the extreme of the genetic-environment continuum, transmitting particularly high rates of illness to their relatives.

However, further studies with larger numbers of probands and relatives within each subgroup are required. The results of this study should be interpreted in the light of several limitations: The assessment of lithium response is subject to methodological bias because it is based on a retrospective assessment, as the illness lasts longer in early onset than in late onset bipolar probands and as the adequacy of dosage was not confirmed by determination of plasma lithium levels. Survival analysis has some methodological limitations because all methods of age correction require the assumption that there is no large changes over time in the age-specific risk for the disorder. This assumption may not be true for psychiatric disorders.

If confirmed, these results may have further implications for future clinical and genetic studies. Indeed, the aim of this study is to disentangle psychiatric disorders by identifying basic phenotypes for which one might expect a more homogeneous etiology. We

argue that identifying more homogeneous forms of diseases according to phenotypic indicators showing good intra familial correlation may yield better results in psychiatric genetics. To confirm this hypothesis, our data are supported by the preliminary results of two association studies performed in the same sample of bipolar patients: (1) an association between a marker of the tyrosine hydroxylase gene and late onset bipolar probands has been reported (Bellivier et al., 1997a); (2) an association between the apolipoprotein E gene (allele $\epsilon 4$) and a subgroup of early onset bipolar probands has also been reported (Bellivier et al., 1997b). The findings presented here may also have implications for linkage studies. Ascertaining families through early onset bipolar probands may help to identify extended pedigrees with high incidence and severity of affective disorders. These families may be more appropriate for genetic analyses than are families of late onset probands.

Acknowledgements

This research was supported by grants from Assistance Publique des Hôpitaux de Paris (Délégation à la Recherche Clinique, CRC 940232), Fondation pour la Recherche Médicale (F.S) and INSERM (Poste d'accueil) (F.B).

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