Journal of Affective Disorders 150 (2013) 993–1000

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Characteristics and profiles of bipolar I patients according to age-at-onset: Findings from an admixture analysis

Jean-Michel Azorin [a,*], Frank Bellivier [b], Arthur Kaladjian [a], Marc Adida [a], Raoul Belzeaux [a], Eric Fakra [a], Elie Hantouche [c], Sylvie Lancrenon [d], Jean-Louis Golmard [e]

[a] Department of Psychiatry, Sainte Marguerite Hospital, Marseilles, France
[b] AP-HP, Université Paris Diderot, Service de Psychiatrie, Hôpital Lariboisière Fernand Widal, Paris F-75010, France
[c] Anxiety and Mood Center, CTAH, Paris, France
[d] Sylia-Stat, Bourg-la-Reine, Paris, France
[e] ER4/EA3974, Dpt de Biostatistiques, Université Paris 6 et APHP, UF de Biostatistiques, GH Pitié-Salpêtrière, Paris, France

ARTICLE INFO

Article history:
Received 26 February 2013
Received in revised form
13 May 2013
Accepted 13 May 2013
Available online 12 June 2013

Keywords:
Bipolar disorder
Age-at-onset
Admixture analysis
Affective disorder

ABSTRACT

Background: Many studies have used admixture analysis to separate age-at-onset (AAO) subgroups in bipolar patients, but few have looked at the phenomenological characteristics of these subgroups, in order to find out phenotypic markers.
Methods: Admixture analysis was applied to identify the model best fitting the observed AAO distribution of a sample of 1082 consecutive DSM-IV bipolar I manic inpatients who were assessed for demographic, clinical, course of illness, comorbidity, and temperamental characteristics.
Results: The model best fitting the observed distribution of AAO was a mixture of three Gaussian distributions. We could identify three AAO subgroups: early, intermediate, and late age-at-onset (EAO, IAO, and LAO, respectively). Patients in the EAO subgroup were more often single young males exhibiting severe mania with psychotic features, a subcontinuous course of illness with substance use and panic comorbidity, more suicide attempts, and temperamental components sharing hypomanic features. Patients with LAO showed a less severe picture with more depressive temperamental components, alcohol use and comorbid general medical conditions. A less typical phenotype was present in IAO patients.
Limitations: The following are the limitations of this study: retrospective design, and bias toward preferential enrollment of patients with manic predominant polarity.
Conclusions: This study confirms that bipolar I disorder can be subdivided into three subgroups based on AAO distribution and shows that patients from these subgroups differ in phenotypes.

1. Introduction

The view that bipolar disorder is a chronic disease with alternating episodes of mania and depression together with free intervals has been gradually overtaken by an understanding of its heterogeneity and the need to identify phenotypic markers associated with subtypes (Leboyer et al., 2005). Age at onset (AAO) has been proposed as a key indicator in delineating more homogeneous subgroups of bipolar disorder patients (Bellivier et al., 2001). A major limitation of earlier studies, however, has been the use of cutoff points, with arbitrary definitions of early and late-onset (Ortiz et al., 2011). Admixture analysis is a statistical method that has been used to overcome this limitation (Celeux and Diebolt, 1990). Applying this method, several authors have suggested that bipolar I disorder aggregate into three age-at-onset subgroups (Bellivier et al., 2011): early age-at-onset (EAO), intermediate-age-at-onset (IAO), and late-age-at-onset (LAO). However, only a few of them (Lin et al., 2006; Manchia et al., 2008; Hamshere et al., 2009; Ortiz et al., 2011; Tozzi et al., 2011) have tried to examine the phenomenological correlates of these different subgroups.

The Epidemiology of Mania (EPIMAN) II-Mille Study represents one of the largest observational studies conducted in patients suffering from bipolar I disorder. This large-scale study offers a unique opportunity to examine specific aspects of this pathology. The aims of the current investigation were therefore, (1) to test whether we could identify, using admixture analysis, comparable AAO subgroups and in that case, (2) to study their main differential characteristics and, (3) to specify typical patient profiles within each of them.

* Correspondence to: SHU Psychiatrie Adultes, Hôpital Ste Marguerite. 13274 Marseille, Cedex 9, France. Tel.: +33 491744082; fax: +33 491745578.
E-mail addresses: jazorin@ap-hm.fr, Jean-michelRoch.AZORIN@ap-hm.fr (J.-M. Azorin).

0165-0327/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2013.05.026

2. Methods

2.1. Study population

Patients included in the study were hospitalized for a manic episode of bipolar I disorder. Diagnosis was made using the French version of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997; Bordeleau, 1997).

2.2. Study design

EPIMAN II Mille, implemented in France, was a multicenter naturalistic study conducted at 19 medical centers between December 2000 and April 2002. The primary aim of the study was to further characterize the validity of the different subtypes of bipolar I disorder and estimate their prevalence in this national clinical sample. Our objective was to enroll 1000 patients. To reach this goal, each of the 317 psychiatrists had to recruit at least two consecutive manic patients (with a maximum of 6). All psychiatrists working in public, university, or private hospitals had considerable clinical experience in studies involving bipolar disorder patients.

2.3. Clinical assessments

At entry, sociodemographic characteristics and illness history were collected, as well as information about psychotropic treatment administered during the previous year. Age at onset was obtained from structured interviews with the patients and their relatives and from their medical records. It was defined as the age at which the patient first met the Research Diagnostic Criteria for an affective episode (Daban et al., 2006; Roy-Byrne et al., 1985); this definition does not necessarily include the presence of psychotic symptoms or a hospitalization.

Intensity of mania was assessed by the Mania State Rating Scale (MSRS) (Beigel et al., 1971; Akiskal et al., 2003); depression, using the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979; Pellet et al., 1981); and psychotic symptoms were recorded on the Scale for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984; Boyer and Lecrubier, 1997).

After marked improvement of the manic episode, on average 21 days from admission, affective temperaments were assessed with the use of 4 questionnaires corresponding to the hyperthymic, depressive, cyclothymic and irritable temperamental components; these tools are self-report, yes-or-no type questionnaires which represent the French version of TEMPS-A (Temperament Evaluation of Memphis, Pisa, Paris and San Diego-autoquestionnaire version) and are designed to quantify temperament in psychiatric patients and healthy subjects (Hantouche et al., 2001); also, lifetime anxious comorbidity was assessed, again using the SCID probes.

The search for associated organic disorders (substance-induced disorders and general medical conditions) was based on a clinician-friendly approach in order to lighten the protocol and facilitate the feasibility of this multi-site investigation. Alcohol and other substance use was defined as "excessive" when it was continued for >1 month in the year preceding mania onset despite social, occupational or psychological problems associated with the substance, it was judged as "moderate" in the other cases; and "no use" when absent. The presence of any general medical condition that might have been diagnosed during the year preceding either illness or current episode onset was checked by interviewing patients, with the help of a medical history form.

Patients were assessed for substance induced disorders at study entry and for general medical conditions, after marked improvement of the manic episode.

From days 1 to 3 following inclusion, patients were requested to keep a daily mood record, with 'best I ever felt' (+5) to 'worst I ever felt' (−5) used as the anchor points and with the midpoint anchored as 'normal' based on validated methodology by Gottschalk et al. (1995). Patients were instructed to complete the scale three times a day (around 8 a.m., 12 p.m. and 6 p.m) by placing an X on the line that best reflected their present mood state in relation to the anchor points. Maximal variation on mood rating was taken as a proxy for mood instability.

Most scales were used in their respective French versions, as validated in our prior EPIMAN study (Akiskal et al., 1998; Azorin et al., 2000). As far as the MADRS and SAPS scales, they had been validated by others as noted above.

The study was reviewed and approved by the appropriate ethics committee, and patients participated with informed, voluntary, written consent.

2.4. Statistical analyses

In a first step, the goal was to determine the number of subgroups according to AAO. We use an admixture analysis, which is a classification method for search the best fit for the distribution of AAO among the models with one or several Gaussian components. The model with one Gaussian distribution is fitted first, and then we repeatedly try to add new components using the following criterion: one component is added if the log-likelihood of the new model, with k+1 components, is greater than the log-likelihood of the former model, with k components, plus half the threshold value of a chi-squared distribution with 3 degrees of freedom and a p-value of .05, that is 7.815. The process of adding new components stops when the new model log-likelihood improvement does not reach the threshold value. For each number of components, the weights, means, and variances of each component were estimated using the stochastic expectation maximization algorithm (Celeux and Diebolt, 1990).

In a second step, the posterior probabilities of each group for each AAO were computed given Bayes formula, which allowed to determine the most probable subgroup for each patient. The patients have been assigned to their most probable subgroup for the further of the study.

Characteristics of bipolar patients were examined for association with onset subgroups. For categorical variables, χ^2 or Fisher's exact tests were used to compare three subgroups: early, intermediate and late onset. For continuous variables, the appropriate tests of analysis of variance (parametric or nonparametric) were used to compare the three groups. For all analyses, if the overall test was found to be statistically significant ($p \leq .05$), pairwise post hoc comparisons were conducted. For pairwise comparisons, Bonferroni correction for multiple comparisons was performed.

Stepwise logistic regression models were then used to identify factors associated with one age at onset subgroup, as compared to the other two (early versus intermediate or late; intermediate versus early or late; late versus early or intermediate). Odds ratios with 95% confidence intervals were used for observed associations.

3. Results

3.1. Patients

We exceeded our goal of 1000 French manic patients and actually recruited a total of 1090 patients. All were bipolar I patients who had experienced manic plus depressive episodes (Bipolar I Disorder, Most Recent Episode Manic or Mixed, according to DSM-IV), to the exception of 82 patients who experienced their first episode of illness (Bipolar I Disorder, Single Manic or Mixed episode). Age at onset was not documented for eight patients. Mean current age was 42.85 ($\pm$ 13.73) years. Of the total population, 42.2% were male. The mean number of prior episodes