Clinical expression of bipolar disorder type I as a function of age and polarity at onset: convergent findings in samples from France and the United States.

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Abstract

Objective: The clinical presentation, course and comorbidities of bipolar disorder type I (BD1) are highly heterogeneous and this variability remains poorly predictable. Certain onset characteristics (e.g. age and polarity at onset) may delineate subgroups differing in clinical expression and outcome.

Method: We investigated the association between both polarity and age at onset and the clinical characteristics of BD1 (DSM-IV), in two independent samples (480 French patients assessed in 1992- 2006 and 714 American patients assessed in 1991-2003).

Results:

Polarity at onset correlated with subsequent predominance ($p<0.001$). Most patients experienced a depressive onset (France: 57.9% and US: 71%; $p<0.001$) associated with a higher density of depressive episodes, suicidal behavior and alcohol misuse. A manic onset was associated with a higher density of manic episodes. Early onset was frequent in both countries (68% in the US versus 42% in France; $p<0.001$) and was associated suicidal behavior, cannabis and cocaine/opiate misuse. Sensitivity for the prediction of clinical characteristics was 1-35% for age at onset and 26-47 % for polarity at onset.

Conclusion: Onset characteristics are associated with subsequent predominant polarity, suicidal behavior and substance misuse in BD1. These findings may facilitate personalized treatment strategies based on type of onset and early focused strategies for preventing comorbidity. Given their relatively low sensitivity and specificity for predicting clinical variables, the relevance of onset characteristics as specifiers in nosographical classifications will require further studies. However, onset polarity may be the more relevant specifier, further investigations being required for age at onset.

Key words: bipolar disorder, onset, polarity, age at onset, clinical expression, course

Introduction

Bipolar disorder type I (BD1) is highly heterogeneous in terms of its clinical expression, course, comorbid psychiatric disorders, comorbid medical conditions and treatment response [1]. The factors underlying this variability are poorly understood. Nevertheless, recent studies have suggested that some onset characteristics, such as age and polarity at the first mood episode, may be associated with different patterns of clinical expression, course and comorbid conditions [2-4]. This may have major implications for the development of preventive strategies, clinical management and drug prescription.

Age at onset (i.e. age at the first major mood episode) is probably the associated factor most widely studied to date (for review see [2]). A threshold at about 21 years of age, defining an early-onset subgroup of the disorder, has consistently been identified in seven independent bipolar I samples from Europe and the USA [5-11]. Early-onset BD1 has been associated with a particular pattern of clinical expression (psychotic features during episodes), a more severe course (rapid cycling) and a higher frequency of comorbid conditions (suicidal behavior, alcohol/substance misuse and anxiety disorders) (for review see [2]).

The polarity of the first episode (i.e. manic or depressive) may also be a relevant factor associated with the course of the disorder. It has been suggested that depressive onset is the most frequent [12-16] and is associated with suicide attempts [12-17], a rapid cycling course [13, 14], comorbid anxiety disorders [15, 18] and axis II comorbid conditions [12]. A manic onset of the disease has been associated with lifetime psychotic symptoms [12, 13, 16], comorbid alcohol misuse [16] and substance misuse preceding onset [12]. Polarity at onset is also of particular

importance because it has been shown to correlate with the predominant polarity of the disease [12-16, 18, 19].

These results have led some authors to suggest that both polarity and age at onset should be added as specifiers in the future DSM-V, given their relevance to both the course and outcome of the disease [3]. Polarity and age at onset have essentially been studied independently, but depressive onset has been associated with an earlier age at onset [14-16, 20, 21]. Thus, to avoid a confounding bias due to these two factors being studied independently, we investigated the relationship between both polarity and age at onset and the clinical, progressive and comorbid expression of BD1 in two well characterized independent samples of BD1 patients from France and the USA.

Methods

Sample of patients (France)

Adult patients meeting DSM-IV criteria [22] for BD1 were recruited from three university-affiliated psychiatry departments and interviewed by trained psychiatrists using the French version of the Diagnostic Interview for Genetic Studies (DIGS) [23, 24]. Patients were of French origin and were euthymic at inclusion (i.e. having MADRS and Mania Rating Scale scores of no more than five) [25, 26]. Written informed consent was obtained from participants. This study was approved by the institutional review board.

Sample of patients (USA)

Clinical data were extracted from the Bipolar Disorder Phenome Database [27]. We selected only BD1 patients, based on the best-estimate diagnosis reported in the database. A

description of the construction of the database, the review of interview items, extraction from the original dataset and quality control of the database has been reported elsewhere [27]. Briefly, bipolar patients were ascertained for genetic linkage studies. Diagnosis was determined with the Schedule for Affective Disorders and Schizophrenia-Lifetime Version [28] or the DIGS [23].

Definition of age at onset

In the French sample, age at onset (AAO) was defined as the age at which the first mood episode occurred (depressive, manic, hypomanic or mixed), according to DSM-IV criteria. It was determined by reviewing case notes and information from the DIGS.

In the American sample, AAO was defined, using the DIGS or the SADS, as the age at which the first DSM-IV criteria manic or depressive episode occurred, on the basis of the fields 'age at first major depression' and 'age at first mania', with the youngest age recorded taken as the age at onset. Hypomanic and mixed onsets were not taken into account because they were not recorded in the database.

Age at onset was classified into two groups: early age at onset (before 21 years) and later age at onset (onset at or after the age of 21 years). This threshold was selected on the basis of the replicated results of seven independent admixture analyses in European and American bipolar type I samples [5-11].

Definition of polarity at onset

In the French sample, two types of onset polarity were defined: depressive onset when the first mood episode met DSM-IV criteria for a major depressive episode, and manic onset when the first mood episode met DSM-IV criteria for a manic, hypomanic or mixed episode.

In the American sample, polarity at onset was determined by comparing the reported age at the first major depressive episode and the age at the first manic episode according to DSM-IV criteria. Subjects for whom the first major depressive episode and the first manic episode occurred at the same age were not included in the analysis. In the American sample, hypomanic and mixed onsets were not taken into account in the definition of polarity at onset because they were not recorded in the database.

Dependent variables

Several clinical categorical and continuous variables were extracted from the two databases (France and USA). Categorical variables (suicidal behavior, mixed episodes, rapid cycling, psychotic symptoms, alcohol/drug misuse, comorbid anxiety disorders) were categorized into lifetime presence *versus* absence. The term 'misuse' defined the abuse of or dependence on substances. For continuous variables, a density measure was obtained by dividing the continuous variable (e.g. number of events) by the duration of the disease (age at interview *minus* age at onset).

Statistical analysis

We investigated the association of demographic and clinical characteristics with both polarity and age at onset. A logarithmic transformation of continuous variables (density of events per year of disease duration) was performed to achieve the normality assumed for parametric procedures. Generalized regression models adjusting for sex were then used to examine relationships between continuous variables and polarity and age at onset as independent variables. Associations between categorical dependent variables and independent variables (polarity and age at onset) were tested by logistic regression with adjustment for sex. As the analysis was exploratory, a *p*-value of 0.05 or less was considered significant. For variables

showing association in both samples, sensitivity (*Sen*) and specificity (*Spe*) were calculated (reported as the area under the curve (AUC) or a percentage). Statistical analyses were performed with SAS software, version 9.1.

Results

Characteristics of the samples

We studied 480 BD1 patients from France and 714 from the USA. The characteristics of the two samples differed significantly for numerous variables (table 1); all differences remained significant when duration was used as a covariate (data not shown).

Depressive onset was associated with an earlier age at onset in the American sample (χ^2 = 20.97, p<0.001), whereas no such association was observed in the French sample (χ^2 = 0.56, p=0.45).

Polarity at onset

Most BD1 patients experienced a depressive onset, and a depressive onset was much more frequent among American patients than among French patients (71% versus 57.9%, respectively; χ^2=21.82, p<0.001).

Several associations were observed in both samples (see table 2). A depressive onset was associated with a higher density of depressive episodes (France: p=0.02 AUC=0.68; USA: p<0.001 AUC=0.61), a lifetime presence of suicidal behavior (France: OR=1.48 95% CI [1.01-2.16] *Sen*=47% *Spe*=63%; USA: OR=1.52 95% CI [1.06-2.17] *Sen*=44% *Spe*=70%) and lifetime alcohol misuse (France: OR=2.08 95% CI [1.28-3.36] *Sen*=26% *Spe*=85%; USA:

OR=1.46 95% CI [1.03-2.08] *Sen*=42% *Spe*=66%). A manic onset was associated with a higher density of manic episodes (p<0.001 in both samples, AUC_{France}=0.59 and AUC_{USA}=0.63).

In the French sample, 61.3% of the mood episodes of bipolar patients who had experienced a depressive onset were major depressive episodes, whereas 60.1% of mood episodes in bipolar patients who had experienced a manic or hypomanic onset were manic or hypomanic. Similar percentages were observed for the American sample (61.3% and 57.8%, respectively). Thus, in both samples, polarity at onset (but not age at onset) was associated with the subsequent predominant polarity of the disease. Indeed, polarity at onset was the only variable found to be associated with this percentage (France: beta=-0.21, 95% CI [-0.26, -0.16], p<0.001; USA: beta=-0.19, 95% CI [-0.23, -0.15], p<0.001).

Some associations were observed in only one sample. A depressive onset was associated with rapid cycling in the French sample only, and with panic disorder and anxiety disorders in the US sample only. A manic onset was associated with a higher density of hospitalizations in the US sample only.

Age at onset

A large proportion of patients belonged to the early-onset subgroup in both the French and American samples (42 % in France *versus* 68 % in the USA; p<0.001).

Several associations were observed in both samples (see table 2). An early age at onset was associated with suicidal behavior (France: OR=2.16 95% CI [1.48-3.15] *Sen*=35% *Spe*=46%; USA: OR=2.05 95% CI [1.44-2.92] *Sen*=27% *Spe*=54%), lifetime cannabis misuse (France:

OR=2.60 95% CI [1.51-4.48] *Sen*=9% *Spe*=79%; USA: OR=1.75 95% CI [1.02-3.01] *Sen*=30% *Spe*=59%) and lifetime cocaine/opiate misuse (France: OR=4.21 95% CI [1.12-15.80] *Sen*=1% *Spe*=95%; USA: OR=2.71 95% CI [1.55-4.73] *Sen*=7% *Spe*=83%).

Some associations were observed in only one sample. An earlier onset was associated with a lower density of hospitalizations in the French sample only. An earlier onset was associated with a higher density of major episode (both depressive and manic), rapid-cycling, alcohol misuse, panic disorder and anxiety disorders in the US sample only.

Discussion

In two large independent samples of BD1 patients, we found that a depressive onset was the most frequent initial presentation of the disease and that polarity at onset was strongly correlated with the predominant polarity. We suggest that age and polarity at onset are associated with particular patterns of clinical expression, disease course and comorbid conditions. Indeed, a depressive onset was associated with suicidal behavior and alcohol misuse and earlier onset was associated with suicidal behavior and cannabis and cocaine/opiate misuse. These findings were obtained in two independent samples with different clinical presentations, recruitment procedures, geographic origins, level of familial/genetic loading, age at onset and duration of illness. Furthermore, slightly different criteria were used to define age at onset and polarity at onset in the two samples. Nevertheless, despite these major differences, we found consistent associations in the two samples. These findings suggest that both age and polarity at onset should be systematically investigated in BD1 patients and could be considered specifiers of the course of the disease, as previously proposed [3].

In both samples, a major depressive episode was the most frequent mode of onset of BD1, as previously suggested [12-14]. Therefore, most BD1 patients will initially be thought to be suffering from a major depressive episode (single or recurrent) before the occurrence of the first manic, hypomanic or mixed episode. This may account for the high estimated rate of misdiagnosis (about 70%) [29-32] and the long delay to treatment in many patients [33]. The awareness of psychiatrists and general practitioners should be increased, to encourage them to explore in detail all possible indicators of a progression towards bipolar disorders when treating a patient suffering from a major depressive episode (particularly when recurrent). Careful screening for certain characteristics of major depressive episodes that have been identified as potential indicators of bipolar disease, and for undiagnosed hypomanic episodes and a family history of BD should immediately trigger suspicion of possible progression towards bipolar disorders [34].

Our second major finding for these two independent samples was the strong correlation between the polarity at onset of the disorder and subsequent predominant polarity, consistent with previous reports [12-15, 18, 35]. Polarity at onset is thought to be familial [21] and underpinned by genetic and/or shared environmental factors, accounting for the notion that polarity at onset reflects a more stable trait (i.e predominant polarity). This may have many implications for treatment. Indeed, the drug treatment strategy to be used could be anticipated early in the course of the disorder on the basis of polarity at onset. Some drugs may be significantly more effective at preventing manic relapses, whereas others may be better at preventing depressive symptoms [36]. Some adjustment of the serum concentrations of mood regulators may also be required, as a function of polarity patterns. Lithium concentrations in the lower part of the therapeutic range may be sufficient for the optimal prevention of depressive episodes,

whereas higher lithium concentrations, within the therapeutic range, may be required for optimal protection against manic/mixed episodes [37-39].

In both samples, depressive onset was associated with suicidal behavior and alcohol misuse, as reported in previous studies [12-17]. An early onset was associated with suicidal behavior and the misuse of cannabis or cocaine/opiates, as previously reported [2, 7, 8]. These findings suggest that careful and precise screening for substance use disorders and risks, and closer clinical monitoring could help to prevent poor outcome (due to alcohol misuse and suicide attempts, in particular) in early onset mood disorders.

This study was subject to several limitations. First, the determination of onset characteristics was based on retrospective assessment and may therefore be subject to recall bias. Second, the definition of polarity and age at onset slightly differed between samples, particularly in terms of the frequency of depressive polarity and early onset. Misclassifications may have occurred for some patients in the American sample, for which hypomanic and mixed-onset episodes were not recorded because they may be difficult to identify retrospectively [13, 15]. Third, some associations were observed only in the American sample and this lack of replication might be due to insufficient power, due to the smaller size of the French sample. Finally, the samples differed in terms of clinical presentation. This may be due to differences in recruitment procedures, geographic origins, level of genetic loading, age at onset and duration of illness. As previously reported [40, 41], BD1 patients from the USA have an earlier onset than patients from France. Indeed, the French sample was a mixture of sporadic and familial cases (60% *versus* 40%), whereas all the American patients had at least one affected sibling; the American sample may therefore have been enriched in early-onset cases [2]. This may appear to be a limitation of the study. However, despite differences between the samples in the

frequencies of depressive and/or earlier onset, several results were consistent between samples. This suggests that the principal associations observed between onset characteristics and subsequent course were robust.

The aim of this study was to determine whether onset characteristics were associated with the subsequent clinical expression of the disorder. The sensitivity and specificity of onset characteristics for predicting clinical variables appeared to be low. Indeed, the sensitivity of age at onset for predicting clinical characteristics ranged from 1 to 35% in the French sample and from 7 to 30% in the American sample. For polarity at onset, sensitivity was higher (26-47 %), with an AUC between 0.59 and 0.68, and specificity was acceptable (63-85%). Given the sensitivity and specificity of each parameter, this suggests that many other factors may affect outcome, including duration of untreated period, the appropriateness of treatment and compliance with treatment. This issue could be addressed, at least in part, by making use of information about current psychotropic treatments and previous treatment sequences, but this information was not available in this study. Moreover, given the differences in sensitivity between the two factors considered, polarity at onset seems to have the better potential as a specifier, further investigations being required for age at onset.

Conclusion

Polarity at onset is associated with subsequent predominant polarity during the course of BD1. Suicidal behavior and substance misuse are associated with both onset characteristics (i.e. a depressive onset and an earlier age at onset). These findings are of particular interest for the identification of more homogeneous subgroups of patients for clinical and research studies, the definition of focused prevention strategies for comorbid conditions and selection

of the optimal and best targeted drugs for treatment. Our findings and those of previous studies provide evidence that onset polarity should be considered as a relevant specifier in future BD1 classifications, as proposed for the DSM-V [3]. Age at onset, given it relatively low sensitivity for predicting clinical variables, requires further investigation to determine its potential relevance as a specifier.

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