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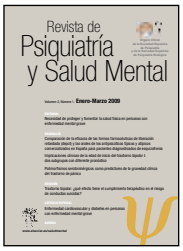

ORIGINAL

Age at onset in bipolar I disorder: two may be better than three subgroups

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KEYWORDS
Bipolar disorder;
Manic depressive illness;
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Abstract

Introduction and objective: Age at onset in bipolar disorder is related to prognosis and to treatment response. However, it is not clear if there are three or two subgroups in relation to age at onset. The objective of this study is to analyze the number of subgroups in relation to age at the beginning of the disease in a representative sample of bipolar I patients and to compare the subgroups in relation to clinical variables.

Method: We included 169 patients diagnosed with bipolar I disorder. Normal mixture analysis was performed. The subgroups of patients formed above were compared regarding clinical characteristics. Patients were followed-up during six years.

Results: We found three ages at onset subgroups. The early onset group (18.2 ± 2 years) included 34% of the patients. The second group (26.1 ± 5.5 years) included 44% of the patients. The third group (50.9 ± 9.1 years) included 22% of the patients. Early and intermediate onset groups were not signifi cantly different, and had more family history of affective disorders, more psychotic symptoms, more history of suicide attempts and more history of drug abuse history than the late onset group.

Conclusions: Our results suggest that there are three groups of age at onset but early and intermediate groups are similar in relation to clinical variables. The late onset group includes almost a quartile of patients and has different clinical profile.

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PALABRAS CLAVE
Trastorno bipolar;
Enfermedad maníaco-depresiva;
Edad de inicio;
Distribución normal;
Historia familia

Implicaciones clínicas de la edad de inicio del trastorno bipolar I: dos subgrupos con diferente pronóstico

Resumen

Introducción y objetivos: La edad de inicio en el trastorno bipolar es crucial para establecer el pronóstico y el tratamiento. Hay una gran controversia sobre si existen dos o tres subgrupos diferenciados de inicio y si éstos difieren lo suficiente como para clasificar la enfermedad en función de su edad de aparición. Nuestro objetivo es agrupar una muestra representativa en función de su edad de inicio, y comparar características clínicas de subgrupos.

Método: Se incluyó a 169 pacientes bipolares tipo I tras firmar el consentimiento informado. Se realizó un estudio de los grupos de edad de inicio mediante un análisis mixto.

Se consideraron antecedentes familiares, intentos de suicidio y síntomas psicóticos. Los grupos obtenidos se compararon con estas variables. El seguimiento duró 6 años.

Resultados: Encontramos 3 subgrupos de edades de inicio. El primero tuvo un inicio a los 18,2 ± 2 años (el 34%de los pacientes). El segundo, a los 26,1 ± 5,5 años (el 44%de los pacientes); el tercero inició a los 50,9 ± 9,1 años (el 22%de los pacientes). Hubo diferencias significativas del tercer subgrupo con respecto a los otros grupos. Los pacientes del primer grupo y el intermedio tuvieron más antecedentes familiares de trastorno bipolar, más síntomas psicóticos e intentos de suicidio y mayor riesgo de historia de consumo de drogas que el grupo de inicio tardío.

Conclusiones: Nuestros resultados indican que hay tres grupos de edad de inicio de trastorno bipolar, aunque pueden agruparse en dos en cuanto a las características familiares, clínicas y pronósticas. Hay resultados diferenciados en el grupo de inicio tardío.

Introduction

The age at onset for bipolar disorder has been fully studied due to the possible prognostic value of this variable and its ability to predict genetically determined subtypes. The age at onset is also important because of the early intervention policies that are now being carried out throughout the Spanish health system. However, an important debate has arisen over what the determining factors are for classifying bipolar disorder into subgroups: for some authors, the fundamental factor for classifying the disorder is the age at onset, while others group the patients according to their clinical characteristics. In fact, no classification system to date considers the age at onset as a factor for grouping clinical subtypes.

We should mention that although the age at onset has been considered in various studies, few studies compare the subgroups and their clinical characteristics. Bellivier et al[1] carried out a study with 211 bipolar I patients from France. These researchers were the first to conclude that the age at onset of the disorder can be classified in three distinct subgroups (early, intermediate, and late onset). This study was of great relevance, and it has led to several later studies that have focussed on clarifying the research team's findings. At a later date, the same team carried out a duplicate of the first study with 368 bipolar patients,[2] and considered it to be new evidence to confirm their three age at onset subgroups.

Nevertheless, Moorhead et al[3] (2003) then carried out a study of 277 bipolar patients and concluded that Bipolar I patients with an age at onset greater than 50 could belong to a different aetiological subgroup. Furthermore, they indicate that the group with no family history of the disorder contains significantly more patients who were first treated after the age of 50.

The present study contributes information regarding the age at onset subgroups that we found in a representative sample of the bipolar I population which includes all patients being treated in the Álava mental health network between 1994 and 1996. The purpose of this study is to group bipolar I patients according to their age at onset and their clinical characteristics that were studied during a six-year follow-up period.

Method

Subjects

The sample's characteristics were described in previous studies.[4,5] It included 169 type I bipolar patients who were first studied between February 1994 and May 1996 in five non-hospital healthcare facilities and one general hospital (98 women, 71 men; average age 46 ± 16 years). At that moment, the sample represented all patients who were receiving treatment within the province of Álava. Santiago Hospital received all patients from an area containing 310,000 inhabitants, and it was the only hospital for acute patients in that area. A psychiatric researcher (AGP) performed the diagnoses using the semi-structured SCID-P interview for DSM IV. The clinical and evolution information was gathered through the interview and from

hospital records, the emergency services, the psychiatrists responsible for patient treatment, the patients' annual review and at least one family member. The patients were included after signing their informed consent.

The clinical variables were gathered in a structured protocol extracted from the SCID-I diagnostic interview for DSM IV,[6] which included data regarding diagnostics, sex, consumption of substances and alcohol and psychotic symptoms. Information on the family history was also gathered using the structured clinical interview RDC-FH, which considers both first-degree and second-degree relatives.[7] Only patients who had at least one family member were included in order to gather that information. In addition, local psychiatric records and emergency services records were used to complete the information.

"Age at onset" is understood as the age of first medical treatment for an affective disorder.

"Suicide attempt" is defined as a self-destructive act that is carried out with the intent to end one's own life. All suicide attempts that were serious enough to require medical attention and hospitalization were included. Both violent and non-violent acts were considered, but most of the suicide attempts involved intoxication with psychotropic drugs.

Suicide attempts were measured both retrospectively and prospectively throughout six years of follow-up. This was also the case for evaluating psychotic symptoms, drug abuse, and the family history of affective disorders.

Statistical analysis

A mixture analysis[8] of the age at onset was carried out according to the method used by Bellivier et al.[1,2] As a first step, we looked for the number of normal distributions of the age at onset present in our sample according to univariate mixture techniques. Secondly, we studied the probability with which a patient would belong to each of the groups with normal distribution that we had identified in the first step. Patients were included in the group in which they had the highest probability of belonging.[8] Therefore, each of the subgroups that we found in the first step constituted a patient subgroup with no overlap between groups, meaning that each patient was included within only one group. For classifying the patients, only age at onset was considered, disregarding all clinical characteristics. We used the Normix[9] application to carry out the analysis. After this, patients were compared according to their clinical characteristics. Multiple logistic regression techniques were used to control comparisons by sex and by duration of the illness.

The assumption that age at onset is a mixture of different normal distributions was examined taking into account the consequence of that assumption, that is, that various age-at-onset subgroups exist. Two statistical tests were used to determine whether or not they are different as regards this consequence. The first is the Dip test of unimodality.[10] By this test, the null hypothesis is that there is only one age at onset group, and the alternative hypothesis is that more than one group exists. The analyses were done using Fortran[11] software. The second test we used was the Silverman unimodality test.[4,12] To analyse the null hypothesis of a single distribution versus the alternative hypothesis of several distributions, we studied the smallest $\hat{h}_1$ window producing a single Gauss distribution. The higher the $\hat{h}_1$ value, the more evidence there is against the null hypothesis. The significance of $\hat{h}_1$ is calculated using the bootstrap method. An SAS IML[13] was designed to carry out the Silverman test. 500 bootstrap samples were used to test the null hypothesis.

Results

The mixture analyses showed three normal distribution groups for the age at onset (fig. 1, comparative test of three and two subgroups, $\chi^2 = 15.1$; d = 3; p = 0.002; four and three, $\chi^2 = 4.2$; df = 3; p = 0.2). Therefore, the sample was classified in three subgroups (early onset, mean ± standard deviation, 18.2 ± 2 years in 34% of the patients; intermediate onset, 26.1 ± 5.5 years in 44% of the patients; and late onset, 50.9 ± 9.1 years in 22% of the patients) (fig. 2). The percentage of women in the early, intermediate and late onset groups was 55, 59 and 61% respectively. The differences in these percentages were not statistically significant ($\chi^2 = 0.39$; df = 2; p = 0.8).

Patients in the early and intermediate onset groups showed no significant differences for any of the clinical variables studied (table 1). Only the late onset group was different from the other two (table 1).

The three types of age at onset found using the mixture analysis do not provide statistically significant evidence

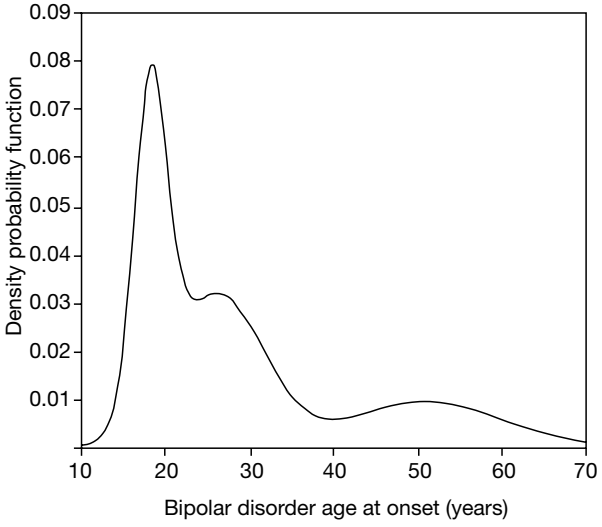

Figure 1 Probability distribution for the age at onset of bipolar patients, assuming that age at onset has a mixed normal distribution. The figure indicates that the age at onset is distributed according to three models. Nevertheless, the statistical tests find that there is no evidence for the existence of more than one model; the assumption is not supported, and therefore, neither is the distribution.

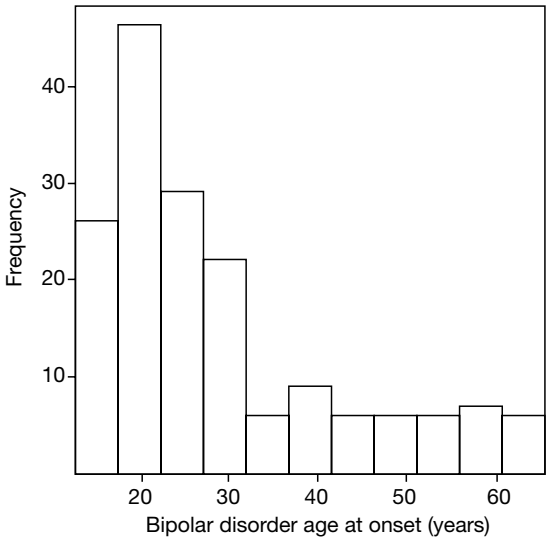

Figure 2 Frequency histogram for the age at onset of the 169 bipolar patients.

with the Dip test or the Silverman test (Dip = 0.035503; $p > 0.05$. Silverman test, $\hat{h}_1 = 5.3432387$; $p = 0.312$). Therefore, it is not possible to confirm the hypothesis that there are three groups with a normal distribution for the age at onset of type I bipolar disorder.

Discussion

We found that the average age at onset for bipolar disorder is distributed in three groups that are relatively similar to those found by Bellivier et al.[1,2] The average ages that we find in our area (18.2, 26.1 and 50.9) are relatively similar to those described by Bellivier in both his first study[1] (16.9, 26.9 and 46.2) and his second study[2] (17.6, 24.6 and 39.2). Nevertheless, although the data for the age at onset do coincide in these two different locations in Europe, the statistical tests that study the consequences of this assumption do not support the existence of three groups with a normal distribution in our study. These results coincide partially with those found by Lin et al[14] (2006) which support Bellivier's study by finding three groups for age at onset in a large sample of bipolar patients (16.6, 26 and 34.7). In this case, the sample was later divided into two groups using 21 years as a reference, and they found that the under-21 group had a higher risk of drug and alcohol abuse.

Furthermore, it is important to mention the statistical tests used in age at onset studies. Mixture analyses assume that a population's age at onset is composed of several subsamples with normal distributions. This assumption is not always justified when looking for biological subtypes.[15,16] For that reason, it is necessary to check if this assumption is correct or not, which frequently has not been done.

Furthermore, when we analyse the age at onset of chronic disorders, such as bipolar disorder, it is absolutely

TABLE 1 **Comparison of subgroups obtained with a normal mixture analysis of the age at onset in 169 bipolar patients**

Group (n)	At least 1 suicide attempt (%)[a,b,c]	History of drug use(%)[b,d]	Psychotic symptoms during mood episodes(%)[b,e]	Family history of mood disorders (%)[f]	Genetic predisposition ratio (mean ± SD)[g,h]
1. Early onset (67)	45	15	87	60	7.6 ± 13.8
2. Intermediate onset (66)	36	12	88	53	5.6 ± 8.7
3. Late onset (36)	19	0	64	39	3.7 ± 6.3

SD: standard deviation; df: degrees of freedom; OR: odds ratio; CI: confidence interval.
[a]Early onset compared with intermediate onset, $c^2 = 0.89$; df = 1; $p = 0.3$. Combined early and intermediate onsets compared with late onset, OR = 2.8; CI, 1.1-6.9.
[b]Values for p and OR adjusted by sex and duration of the disorder.
[c]Suicide data was gathered during six additional years, which guarantees a follow-up period of at least six years from onset for all patients.
[d]Early onset compared with intermediate onset, $c^2 = 0.11$; df = 1; $p = 0.7$. Combined early and intermediate onsets compared with late onset, OR = 11; CI, 1.7+INF.
[e]Early onset compared with intermediate onset, $c^2 = 0.005$; df = 1; $p = 0.9$. Combined early and intermediate onsets compared with late onset, OR = 5.4; CI, 2.1-13.9.
[f]Early onset compared with intermediate onset, $c^2 = 0.6$; df = 1; $p = 0.4$. Combined early and intermediate onsets compared with late onset, OR = 2; $c^2 = 3.5$; df = 1; $p = 0.06$.
[g]Early onset compared with intermediate onset, Mann-Whitney, $p = 0.4$. Combined early and intermediate onsets compared with late onset, Mann-Whitney, $p = 0.05$.
[h]Genetic predisposition ratio = number of relatives with mood disorders divided by number of known family members and multiplied by 100.

necessary to check the duration of the disease when comparing clinical variables. This is particularly relevant for variables such as suicide attempts, since it is obvious that the patients with an illness less developed are less likely to have attempted suicide. In this sense, transversal studies or short follow-up studies are unlikely to detect suicide attempts in patients with late onset, which can significantly alter the results of the investigation. Our study verified the duration of the disorder and followed up on patients over six years to improve the quality of the study.

Clinical analysis by subgroup would provide better support for the existence of two different ages of onset. The reality is that the early onset and intermediate onset groups are very similar across all studied variables. This also occurred in the Bellivier et al study.[1,2] However, the late onset group displays fewer psychotic symptoms, less presence of family history and fewer suicide attempts. Our results also coincide with those found by Moorhead et al.[3] In a sample of 237 patients with type I bipolar disorder, they found that non family-related bipolar disorder included more subjects older than 50 years.[3] We did not find differences in this respect between men and women, as was the case in the English study,[3] but it was not supported by a German sample of bipolar I patients. In that study of 217 German patients, it was found that women without a family history of the disorder had a later age at onset, while no difference was found in the male group.[17]

The early-intermediate age at onset represents a group of patients with more severe symptoms than the late onset group displays. In fact, it has already been described that an early age at onset presents a higher risk of suicide, more substance abuse[5] and incongruent psychotic symptoms.[18]

In conclusion, although we find that there are three different ages of onset, no evidence shows that there are three subgroups with a normal distribution. Furthermore, it is even more relevant that there are no clinical differences that would support classification in three subgroups; rather, it seems more fitting to work with two age-at-onset groups, early-intermediate onset and late onset which would begin in the late 40s or early 50s. This group has different clinical characteristics (fewer psychotic symptoms, less history of substance abuse) a different prognosis (fewer suicide attempts) and aetiology (less family history). Our study has various strengths and limitations. Its principal difference from previous studies is that the group represents bipolar patients from one area and we have prospective follow-up data for the clinical variables. Regarding its limitations, there is probably a sizeable group of bipolar patients who were not receiving psychiatric treatment in a specific period, and who therefore were not included in the study. It is possible that these patients not receiving treatment, who would not be represented in most studies carried out with clinical samples, would have less severe disorders. Nevertheless, our data allows us to state with a certain degree of assurance that age at onset is a variable that is fundamentally important to the treatment and prognosis of bipolar disorder, and that two subgroups may be better than three.

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