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Research paper

Clinical characterization of rapid cycling bipolar disorder: Association with attention deficit hyperactivity disorder

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ABSTRACT

Background: Rapid cycling (RC) bipolar disorder (BD) is associated with more disability and worse global functioning than non-rapid cycling BD (NRC) and is understudied. This study aims to investigate clinical characteristics associated to RC in a Latin-American sample and secondarily, to generate a clinical model to test the likelihood of RC in BD.

Methods: 250 BD patients were enrolled between 2007 and 2015. All patients met DSM-IV criteria for BD type I, II or NOS. The sample was dichotomized into RC and NRC subgroups, and compared in terms of socio-demographic and clinical variables by bivariate analyses. A binary logistic regression was performed to generate a model and explain variance associated with the likelihood of presenting RC.

Results: Final sample included 235 patients, of which forty-four (18.7%) met RC criteria. When compared to NRC, a significantly higher proportion of RC patients were female (81.4% vs. 58.9% $p = 0.006$), BD type II (58.1% vs. 29.7% $p = 0.002$), presented more manic/hypomanic episodes (43.6 ± 35.8 vs. 12.8 ± 58.9, $p = 0.001$), and had less psychotic symptoms (20.9% vs. 42.2%, $p = 0.010$). Attention deficit hyperactivity disorder (ADHD) was a significant comorbidity in RC (23.7% vs. 8.3%, $p = 0.007$). No differences were found in suicidality, mixed symptoms, and seasonal pattern. After logistic regression, variables significantly associated with RC were presence of ADHD (OR 4.6 [95% CI 1.54–13.93] $p = 0.006$) and female gender (OR 3.55 [95% CI, 1.32–9.56] $p = 0.012$).

Limitations: It is a cross-sectional study.

Conclusions: Findings suggest that ADHD comorbidity, and female gender are risk factors for RC in BD.

1. Introduction

Bipolar affective disorder (BD) represents a challenge to health systems, due to its chronic, episodic and recurrent condition (Vieta et al., 2018). There is consensus in the most important diagnostic classifications regarding the clinical characteristics of the episodes of BD (i.e. manic, hypomanic, depressive) (American Psychiatric Association, 2013; World Health Organization, 1992). However, the temporality of such episodes is often difficult to specify, because the course of BD is rarely clear, symmetrical and typical (Carvalho et al., 2014).

Bleuler in 1911, and Kraepelin ten years later, made efforts to define the clinical presentation of BD (i.e. manic-depressive illness), and the association between the course and duration of acute mood episodes and their prognosis (Kraepelin, 1921; Zis and Goodwin, 1979). In the early 70s, a worse prophylactic outcome with lithium was noted in patients with a high frequency of acute affective episodes, and since then, the concept of *rapid cycling* (RC) -defined as the presence of four or more episodes of illness within a year- (Dunner and Fieve, 1974) remains valid as a course specifier for BD (American Psychiatric Association, 2013).

The estimated lifetime prevalence of RC in BD patients may reach 32% (Carvalho et al., 2014), yet little is known about its pathophysiology (Buoli et al., 2017; Munkholm et al., 2015). RC patients present more disability (Schneck et al., 2004; Vieta et al., 2013) and worse global functioning than non-rapid cyclers (NRC) (Mackin, 2005; Schneck et al., 2004). From a clinical perspective, previous literature reports an association between RC and an earlier onset of BD (Azorin et al., 2008; Ernst and Goldberg, 2004; Ortiz et al., 2011), greater number of episodes and hospitalizations (Bauer et al., 1994; Coryell

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et al., 2003; Kupka et al., 2003), worse response to pharmacotherapy (Tondo et al., 2003; Vieta et al., 2013), poly-therapies for long-term clinical stabilization (Schneck et al., 2008; Wells et al., 2010), and a higher risk for suicide attempts (Azorin et al., 2008; Bobo et al., 2018; Garcia-Amador et al., 2009; Undurraga et al., 2012).

RC is transient in a significant number of patients, so that assessing clinical correlates may be complicated (Bauer et al., 2008; Fountoulakis et al., 2013; Koukopoulos et al., 2003). Hypothyroidism (Bartalena et al., 1990; Bauer et al., 2008; Cowdry, 1983; Kusalic, 1992), female gender (Bauer et al., 1994; Kupka et al., 2003; Tondo et al., 2003; Wehr et al., 1988; Yildiz and Sachs, 2004) and the use of antidepressants (Pacchiarotti et al., 2013; Valentí et al., 2015; Wehr et al., 1988) were repeatedly associated with RC, but only in small cohorts, supporting that causality between RC course and clinical variables still remains unclear (Carvalho et al., 2014).

In summary, RC in BD represents a big burden to patients, their families and the health system, as it is associated with more disability and worse global functioning. It is an understudied condition, and many of its clinical characteristics and associations remain unclear or controversial. Thus, more studies are need in order to clarify clinical factors associated with this specifier of BD.

The aim of the present study was to investigate clinical characteristics associated to RC in a Latin American sample of patients with BD, and secondarily to generate a clinical model to test the likelihood of RC in BD.

2. Methods

2.1. Study design and participants

A cross sectional study, with data from a prospective cohort of patients in a specialized unit between January 2007 and December 2015.

Patients were recruited by the Bipolar Disorders Unit at Red de Salud UC-Christus, which is a University Hospital located in Santiago, Chile. We included adult outpatients (≥18 years), with a diagnosis of BD type I, II or not otherwise specified (NOS), using a Structured Clinical Interview for Diagnostic and Statistical Manual-Fourth Edition Axis I Disorders according to DSM-IV-TR criteria (American Psychiatric Association, 2000); we excluded patients unable to understand the purposes of the study.

The database was used anonymized throughout the study period, according to local privacy laws. The study protocol was approved by the University Research Ethics Committee.

2.2. Clinical assessments

Data collection was based on combined clinical assessments and structured interviews (Spanish version of the Structured Clinical Interview for DSM-IV Axis I Disorders, **SCID**-I and a semi-structured evaluation at baseline) performed by senior psychiatrists of the Bipolar Disorders Unit, family or care-giver semi-structured interviews, and review of medical records. During the follow-up period, all the episodes were registered.

Collected data included the following sociodemographic and clinical variables: Age, marital status, educational level, family history of psychiatric illness, presence of traumatic events, peripartum mood disturbances, age at onset of BD, duration of untreated illness (DUI, defined as the time elapsed between the age at diagnosis of BD (according to DSM-IV TR criteria) and administration of appropriate treatment and the age when the patient presented his first affective episode (Altamura et al., 2011), number and duration of hospitalizations, switch associated with antidepressants (Tohen et al., 2009), comorbidity with other psychiatric disorders, according to DSM-IV criteria, lifetime presence and type of substance use disorder. Recorded clinical specifiers of BD include mixed features, psychotic symptoms, seasonal pattern, duration and polarity of lifetime episodes (Baldessarini et al., 2012; Colom et al., 2006), and suicide attempts. Previous and current pharmacological and electroconvulsive therapy details were also recorded.

Rapid Cycling was defined as the presence of at least 4 mood episodes in the prior year, according to DSM-IV criteria (American Psychiatric Association, 2000).

2.3. Data analyses

The sample was dichotomized into RC subgroup and non-RC subgroup. The two subgroups were then compared with bivariate analyses. Quantitative variables were compared by analyses of variance (ANOVAs) while qualitative variables were compared by chi-square tests (χ^2). We adjusted for multiple comparisons using Bonferroni correction (0.05/173) requires $p < 0.003$).

Factors outlining significant differences between the 2 subgroups (RC vs. non-RC) in this preliminary bivariate analysis, or considered clinically relevant were then tested for independent and significant association with RC using logistic multiple regression modeling to explain their possible contribution to the variance of the model, expressed as odds ratios (ORs) and their 95% confidence intervals (CI).

Statistical analyses were conducted using the software Statistical Package for Social Sciences version (IBM Corp. Released 2011. IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, NY: IBM Corp).

3. Results

3.1. Total sample

A total of 250 patients were initially recruited, of which 15 were excluded, because they did not complete the minimum clinical assessments required. Therefore, the final sample included 235 patients: 87 males (37%) and 148 females (63%). 151 (64%) were BD type I, 82 (35%) BD type II, and 2 (1%) BD NOS patients. Age at recruitment was 37.6 years (SD 13.65). Mean age at onset was 22.4 years (SD 10), with a latency time to diagnosis of 7.5 years.

A summary of sociodemographic variables of the total sample is reported in Table 1.

3.2. Bivariate analyses

In our sample, 44 patients (18.7%) met criteria for RC specifier. The proportion of women in the RC group was significantly higher than men (81.4% vs. 58.9% $p = 0.006$), and RC was more associated with BD type II than type I (58.1% vs. 29.7% $p = 0.002$).

In addition, RC patients had an earlier age at onset (19.8 vs. 22.9 years $p = 0.063$) and -by definition- presented more affective episodes compared to the non-RC patients (88 ± 12.7 vs. ± 76.9, $p = 0.003$). The number of manic/hypomanic episodes was significant higher in the RC subgroup (43.6 ± 35.8 vs. 12.8 ± 58.9, $p = 0.001$). Finally, RC patients were associated to a lower proportion of psychotic symptoms than Non-RC (20.9% vs. 42.2%, $p = 0.01$).

On the other hand, RC patients had a greater proportion of mixed symptoms, which was not significant (44.2% vs. 29.2%, $p = 0.056$), and we found no differences in seasonality (34.9% vs. 20.9%, $p = 0.051$), predominant polarity, suicidality, illness duration, hypothyroidism, obesity, or diabetes mellitus.

Regarding psychiatric comorbidity, ADHD was significantly more prevalent in RC than Non-RC patients (23.7% vs. 8.3%, $p = 0.007$).

A summary of differences between subgroups is provided in Table 2.

In multivariate logistic regression modeling, factors that remained significantly and independently associated with RC were studied: gender, BD type, psychotic symptoms, ADHD and total manic/hypomanic episodes (Table 3). The model as a whole was significant [$\chi^2 = 22.93$; df 5, $p < 0.001$], explained 17.1% of variance (Nagelkerke R^2) in rapid cycling and correctly classified 81.1% of cases.

Table 1
Sociodemographic data.

	Number of subjects	Percent (%)
Female	148	63
Male	87	37
Marital Status		
- Single	127	54
- Couple	80	34
- Divorced	22	9
- Widowed	2	1
- Not defined	4	2
Educational Level		
- Incomplete Primary	3	1
- Primary	6	3
- Secondary	111	47
- Universitary	114	49
- Not defined	1	0
Family History (FH)		
- Bipolar Disorder	130	55
- Major Depression	141	60
- Alcohol Abuse	87	37
Lifetime Psychiatric Comorbidity		
- Anxiety Disorders	54	23
- Substance Use Disorders	61	26
- Personality Disorders	77	33
Life Trauma	58	25
Suicide Attempts	50	21

Table 2
Comparison between RC and non RC patients. Significance with Bonferroni correction (0.05/17) requires $p < 0.003$.

Variable	Total N	Non RC N (%)	RC N (%)	χ^2/ F	p-value
BD type	235			12.706	0.002
- Type 1	151	133 (69.3)	18 (41.9)		
- Type 2	82	57 (29.7)	25 (58.1)		
Gender	235			7.656	0.006
- Female	148	113 (58.9)	35 (81.4)		
- Male	87	79 (41.1)	9 (18.6)		
Hypothyroidism	78	60 (31.6)	18 (41.9)	1.664	0.197
Diabetes Mellitus	18	16 (8.3)	2 (4.7)	0.673	0.412
Obesity	43	37 (19.3)	6 (14.0)	0.664	0.415
Life Trauma	58	44 (24.6)	14 (35.0)	1.823	0.177
Psychotic Symptoms	90	81 (42.2)	9 (20.9)	6.718	0.010
Mixed Symptoms	75	56 (29.2)	19 (44.2)	3.647	0.056
Seasonal Affective D.	55	40 (20.9)	15 (34.9)	3.794	0.051
Suicidality	142	111 (57.8)	31 (72.1)	2.996	0.083
ADHD	23	14 (8.3)	9 (23.7)	7.363	0.007
Predominant Polarity	144			0.208	0.648
- Depressive	70	57 (49.6)	13 (44.8)		
- Manic	74	58 (50.4)	16 (55.2)		
CONTINUOUS VARIABLES	Mean (SD)				
Age at Onset	22.4 (10)	22.9 (10.4)	19.8 (7.5)	3.498	0.063
Total Episodes	39 (122)	28 (12.7)	88 (76.9)	8.809	0.003
Manic/hypo Episodes	18.4 (56.6)	12.8 (58.9)	43.6 (35.8)	10.863	0.001
Depressive Episodes	20.6 (75.7)	15.2 (78.7)	44.4 (55.4)	5.318	0.022
Illness Duration (years)	15.3 (10.3)	15.3 (10.4)	15.1 (10.2)	0.018	0.894

Table 3
Multivariate logistic regression of factors associated with RC.

Factor	Wald χ^2	Odds Ratio (95% CI)	*p*-value
Female	6.26	3.55 (1.32–9.56)	0.012
BD Type 2	0.41	1.39 (0.50–3.79)	0.524
Psychotic Symptoms	0.84	0.63 (0.23–1.69)	0.361
ADHD	7.42	4.6 (1.53–13.92)	0.006
Manic/hypo Episodes	0.46	0.93 (0.75–1.14)	0.497

Variables included in the model: gender, bipolar type (1 vs. 2), psychotic symptoms, ADHD, Manic or hypomanic episodes.
The model was significant [$\chi^2 = 22.93$; df 5, $p < 0.001$], explained 17.1% of variance (Nagelkerke R^2) in rapid cycling and correctly classified 81.1% of cases.

Significant variables after logistic regression, were the presence of ADHD (OR 4.6 [95% CI 1.54–13.93] $p = 0.006$) and female gender (OR 3.55 [95% CI, 1.32–9.56] $p = 0.012$). That is, bipolar patients with a previous history of ADHD are 4.6 times more likely to manifest a rapid cycling course than patients without a history of ADHD, and female bipolar patients are 3.6 times more likely to exhibit rapid cycling than males.

4. Discussion

In this cross-sectional study, conducted on a Latin-American sample of BD patients, we found that bipolar patients with a previous history of ADHD or female, are more prone to exhibit rapid cycling.

Previous history of ADHD in BD patients was significantly associated to RC course (OR 4.6 [95% CI 1.54–13.93]). Awareness on the comorbidity between ADHD and BD patients is relatively recent (Nierenberg et al., 2005; Tamam et al., 2008; Torres et al., 2015; Wingo and Ghaemi, 2007). Reported lifetime prevalence of ADHD in bipolar illness ranges from 9.5 to 37.8% (Karaahmet et al., 2013; Schneck et al., 2008), and a lifetime ADHD prevalence 9.78% in our sample is consistent with this data.

Clinical characterization of ADHD-BD comorbidity is still scant and comes mostly from children and adolescent samples. Comorbidity between these disorders has been associated with an earlier onset of BD, increased impulsivity, presence of mixed symptoms, greater number of suicide attempts and a significant comorbidity with substance misuse, with a consequent functional impairment (Nierenberg et al., 2005; Rydén et al., 2009; Torres et al., 2018, 2017). Interestingly, ADHD unique comorbidity in BD is not associated with very early-onset of BD (Propper et al., 2015), so that if confirmed, the finding of an association between both ADHD and RC in our adult population is specific, and reported (to our knowledge), in just one previous cross-sectional study (Lee et al., 2010). Nevertheless, the possibility that this finding is an artefact must be acknowledged, as manic-like symptoms and RC/ultra-RC diagnosis in ADHD pose a difficult differential diagnosis between the two conditions (Faraone et al., 2001; Wozniak et al., 1995).

The clinical occurrence of elevated mood instability, cognitive symptoms and impulsivity delineates a specific clinical phenotype which deserves special attention, in order to address both conditions. A recent systematic review on current evidence of the use of stimulants in BD-ADHD patients concluded that ADHD should be addressed after a sustained stabilization of BD, and stimulants should be used always in combination with mood stabilizers (Perugi et al., 2017).

In our study, female gender was also strongly associated with RC (OR 3.55 [95% CI, 1.32–9.56]), coherently with previous findings (Baldassano et al., 2005; Bauer et al., 2008). A study recently conducted on a large sample of 1,225 BD patients showed a significant association between female gender and increased risk of RC, independent of other known risk factors (Erol et al., 2015). Three possible explanations have been proposed: Firstly, a relation with thyroid dysfunction, which relies on contradictory evidence (Bartalena et al., 1990; Bauer et al., 2008;

Cowdry, 1983; Joffe et al., 1988; Kusalic, 1992). Yet, we did not find an association of RC and thyroid dysfunction in our study. Secondly, use of antidepressants is more frequent in female BD patients, and this has been associated with an increased risk of RC (Ghaemi et al., 2010; Wehr et al., 1988). Moreover, recommendations coming from a consensus of international experts suggested avoiding antidepressant treatment in RC-BD patients for this reason (Pacchiarotti et al., 2013). These opinions found further ground on solid evidence in a recent randomized-controlled trial showing a significant increase of mood episodes during the first year of follow-up in patients with RC-BD (particularly with depressive recurrences), using new generation antidepressants in combination with mood stabilizers (El-Mallakh et al., 2015). Thirdly, women are more prone to depressive polarity and may be more likely to seek help and receive treatment for depression, so the possibility of being diagnosed as RC is higher than men (Calabrese et al., 2001; Cruz et al., 2008). However, the relation between female gender and RC has not been a consistent finding (Carvalho et al., 2014; Nivoli et al., 2011). One possible reason for this conflicting evidence may be the fact that RC is difficult to study in clinical practice due to its transitory nature during the course of BD.

In our sample, RC patients presented a greater number of manic/hypomanic episodes when compared with non-RC patients. This was an unexpected finding, as current evidence supports the association between RC and greater number of depressive episodes rather than manic/hipomanic (Carvalho et al., 2014; Coryell et al., 2003; Lee et al., 2010; Schneck et al., 2008). However, we found one previous prospective evaluation of 539 outpatients with BD, showing a greater frequency of manic episodes in RC when compared to non-RC patients (Kupka et al., 2005). A possible explanation for our finding, might be the overrepresentation of type I BD patients in our sample (64.25%), which could be related to the fact that recruitment was done in a specialized unit. Another possible explanation could be that this is a sample of Latin-American patients. Studies conducted in the US, show that Latin-American patients have different risks for diverse health conditions, for example, metabolic syndrome in psychosis (Kato et al., 2004). This could be due to biological differences such as genetic inheritance, but also by social determinants such culture, access to healthcare, disparities in treatment and service utilization, among others (Ralat et al., 2017; Salcedo et al., 2017; Stein et al., 2017). This could explain some differences with previous research on rapid cycling, and might limit the generalizability of the results. Latin-American subjects are generally underrepresented in the scientific literature (Patel & Kim, 2006). This knowledge may aid in better understanding the nature of bipolar disorders and developing more effective social policies to prevent these disorders and promote mental health to all the population.

5. Limitations and strengths

The cross-sectional nature of this study design limits its ability to draw conclusions about causality, because risk factors and outcomes are measured simultaneously. The sample size of the study sample cannot rule out type II errors. Also, the present study was conducted in an academic specialized unit, which might be a limitation to the generalization of the results, as it is likely that our patients represent more severe cases. In addition, the aim of this project was to investigate clinical characteristics associated to RC in BD patients. The association between ADHD and BD was not a priory and specifically hypothesized. Therefore, we included ADHD as a lifetime diagnosis reported by the patient, care-givers or the medical record (using DSM-IV-TR criteria), which could lead to underreporting and recall bias.

On the other hand, this study has strengths that deserve mention, such as rigorous clinical characterization of the sample operated by specialized psychiatrists using structured interviews, family interview and review of medical records, to ensure high quality to our clinical data.

6. Conclusions and future research

In conclusion, our study outlines a strong association between RC, ADHD, and female gender. Clinicians should carry out careful diagnostic assessments in order to point out possible areas of interventions for comorbidity, for instance, addressing specific deficits in attention and concentration, as well as aiming at mood stabilization and cycle reduction.

Larger studies with prospective designs should be targeted at defining clinical subgroups of patients affected by bipolar disorder with proneness to develop rapid cycling at some moment in their course of illness. They will permit to establish incidence and a more solid temporal relation between exposures (e.g. ADHD, female gender, perhaps hypothyroidism as previously described) and rapid cycling. Genetic liability to rapid cycling and other biological markers should be extensively researched as well. Last, refractoriness to treatments is a common issue in rapid cycling bipolar disorders, so that preventive strategies should be developed and be included in the treatment plan of this subset of patients.

Authors' contributions

AE and JU designed the study and wrote the protocol. AE, AM, RS, IG, EV and JU retrieved the data and performed the analyses. AE wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

The funding sources had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Conflicts of interest

AM has received Continuing Medical Education-related honoraria or consulting fees from Adamed, AstraZeneca, Bristol-Myers-Squibb, Janssen, Lundbeck, and Otsuka. **IG** has served as a consultant for Ferrer, advisor for Lundbeck, Otsuka and has been a speaker for Ferrer, Janssen and Lundbeck, Otsuka. **EV** has received grants and served as a consultant, advisor, or CME speaker for the following entities: AB-Biotics, Allergan, AstraZeneca, Bristol-Myers-Squibb, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Telefonica, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (Centro de Investigación Biomédica en Red de Salud Mental), the Seventh European Framework Programme (European Network of Bipolar Research Expert Centres), and the Stanley Medical Research Institute. The other authors report no potential conflicts of interest in the material presented.

All authors made substantial contributions and approved the manuscript as submitted.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.07.051.

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