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Clinical differences between patients with pediatric bipolar disorder with and without a parental history of bipolar disorder

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ABSTRACT

Pediatric Bipolar Disorder (PBD) is a highly heritable condition responsible for 18% of all pediatric mental health hospitalizations. Despite the heritability of this disorder, few studies have assessed potential differences in the clinical manifestation of PBD among patients with a clear parental history of BD. Additionally, while recent studies suggest that attentional deficits are a potential endophenotypic marker of PBD, it is unclear whether heritability is a relevant contributor to these symptoms. In order to address this gap, the present study assessed 61 youth with PBD (6–17 years old), corresponding to 27 offspring of BD patients, and 31 PBD patients without a parental history of the disorder. All standardized assessments, including the K-SADS-PL-W were performed by trained child and adolescent psychiatrists. We performed a logistic multivariate model using the variables of ADHD, rapid cycling, and lifetime psychosis. Rates of ADHD comorbidity were significantly higher among PBD patients who had a parent with BD. Furthermore, PBD patients who had a parent with BD showed a trend toward significance of earlier symptom onset. PBD offspring did not show increased rates of suicide attempts, rapid cycling, or psychosis. Given these findings, it appears that PBD patients who have a parent with BD may represent a distinct endophenotype of the disorder. Future longitudinal and larger studies are required to confirm our findings.

1. Introduction

Bipolar spectrum disorders have a prevalence rate of approximately 2% worldwide (Goldstein et al., 2017), and are associated with a high global burden of disease (Gore et al., 2011). Similar prevalence rates occur among pediatric cases, which causes significant impairment in child development. Indeed, Pediatric Bipolar Disorder (PBD) is responsible for approximately 18% of all pediatric mental health hospitalizations (Bardach et al., 2014; Connor et al., 2017). PBD is also associated with severe medical comorbidities, including premature cardiovascular disease, obesity, suicide, and cognitive dysfunction, which occurs irrespective of mood episode or euthymia (Elias et al., 2017; Goldstein et al., 2017; Passos et al., 2016a).

Current evidence suggests that PBD is a highly heritable disorder with a complex polygenic inheritance (Arnold et al., 2012; van Hulzen et al., 2017). First-degree relatives of BD patients have a 10-fold greater risk of developing BD than the general population. In addition, BD patients with a family history of the disorder have more manic and depressive episodes when compared to BD patients without a family history of the disorder (Duffy et al., 2017). Given the large degree of heterogeneity inherent to bipolar disorder (Kapczinski et al., 2017), a greater focus on characterizing illness trajectories is warranted (Cao et al., 2017; Duffy et al., 2017a).

Previous studies have assessed the trajectories of BD offspring (Duffy et al., 2011, 2000). Of note, offspring of patients who do not respond to lithium show greater prevalence of attention deficit hyperactivity disorder (ADHD), learning disabilities, distorted thinking patterns, and difficulty with impulse control, relative to offspring of lithium responders (Duffy et al., 2014). Similarly, offspring of parents with BD show an 8-fold greater risk of developing ADHD, and present with higher rates of behavioural disinhibition, hyperactivity, emotional dysregulation, as well as disruptive and depressive symptoms (Birmaher et al., 2010). Moreover, BD offspring present with greater externalizing, inattention/disinhibition, subsyndromal manic and

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affective lability symptoms (Lau et al., 2018; Van Meter et al., 2016). Of note, among BD offspring there appears to be a significant overlap in externalizing inattention/disinhibition symptoms, which are hallmark characteristics of ADHD (Gallo and Posner, 2016; Shaw et al., 2014).

PBD is a heterogeneous disorder, and a further analysis of relevant subtypes is warranted in order to aid in the development of tailor-made interventions (da Costa et al., 2016; Duffy et al., 2016; States and Control, 2018). Several studies have investigated early onset BD (Goldstein et al., 2017). Of note, Soumin et al., (2007), used a representative cohort to assess differences between 191 inpatients and outpatients with early vs. adult BD. Early-onset BD patients were shown to have more severe illness trajectories and clinical features (Suominen et al., 2007). Moreover, the clinical trajectories of high-risk offspring without BD have been well-documented (Doucette et al., 2016; Duffy et al., 2017b). Considering the available evidence, as described above, assessing early onset BD among high-risk individuals represents a promising avenue to further explore differences in illness trajectories within BD.

The present study aims to assess the clinical differences between offspring and non-offspring with PBD, including ADHD comorbidity. Moreover, we will assess known risk factors of poor prognosis in BD, including suicide attempts, rapid cycling, psychosis and age of onset. We hypothesize that increased ADHD comorbidity and poorer clinical outcomes such as suicide attempts, psychosis and rapid cycling will be more prevalent among PBD patients with a family history of BD.

2. Methods

2.1. Participants

The present cross-sectional study comprises 61 children and adolescents (6-17 years old) with PBD, recruited from the Outpatient Program for Children and Adolescents with Bipolar Disorder (ProCAB) at the Hospital de Clínicas de Porto Alegre, Brazil. Data were collected between January 2015 to January 2018. Eligible patients were younger than 18 years old and were diagnosed with either BD I, II, or not otherwise specified (NOS), according to DSM-IV Criteria (American Psychiatric Association, 2000). Exclusion criteria were IQ under 80, and diagnosis of either schizophrenia, pervasive developmental disorder, or substance dependency/abuse. All patient assessments were conducted in the presence of parents/caregivers. A total of eight patients were excluded from the study, corresponding to seven that lacked full criteria for PBD, and one had an IQ under 80.

2.2. Procedures

2.2.1. Ethical considerations and screening

The study was approved by the Institutional Ethics Committee of Hospital de Clínicas de Porto Alegre (Protocol 07641). Written informed consent was obtained from parents or caregivers, and verbal assent was obtained from the participants. Once consent was obtained, parents or caregivers underwent a screening interview, where DSM-IV mood symptoms and family history of psychiatric disorders were clinically assessed by a child and adolescent psychiatrist.

2.2.2. Diagnosis

Subsequently, both participants and caregivers were interviewed using the St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL-W) (Geller et al., 1994, 2001) by trained research staff. The K-SADS-PL-W (Geller et al, 1994, 2001), a semi-structured interview used to screen for affective and psychotic disorders, was used to assess diagnosis and comorbidities in participants. A trained child and adolescent psychiatrist also performed a clinical evaluation to assess diagnosis and comorbidities, and in cases of disagreement (K-SADS and clinical assessment), a committee of specialists would meet to discuss the definitive diagnosis.

2.2.3. Demographic, clinical and cognitive assessment

Clinical and sociodemographic information were collected by self-report, which included age, sex, race, family income, the age of symptom onset, psychotic features, bipolar subtype, current manic or depressive episode, mother's education, and the number of previous hospitalizations. Family history of psychiatric disorders was assessed using a self-report questionnaire created by our research team for parents and siblings. Participants IQ was assessed by a licensed psychologist using the vocabulary and block design subtests of the Wechsler Intelligence Scale, third edition (WISC-III) (Wechsler, 2002). Symptoms of suicide attempts and sucidality were assessed using the K-SADS PLW suicide section.

Manic symptoms were assessed using the Young Mania Rating Scale (YMRS) (Young et al., 1983), with clinically relevant mania defined as scores $\geq$ 12 (Vilela et al., 2005; Yee et al., 2015) Depressive symptoms were assessed using the Children's Depression Rating Scale (CDRS-R) (Poznanski et al., 1985), an instrument widely used in clinical studies to measure depressive symptoms in children and adolescents. In the CDRS-R, scores >40 are indicative of depression, while scores ≤ 28 are often used to characterize remission (Cardoso et al., 2017). All instruments used were validated in Portuguese (Graeff and Vaz, 2008; Vilela et al., 2005).

Additional measures included the Clinical Global Impression (CGI) rating scale, severity subscale (CGI-S) and the Children's Global Assessment Scale (CGAS). The CGI is used to characterize the severity of a patient's illness at the time of assessment (Busner and Targum, 2007). The CGAS is a 100-point scale used to measure general functioning in children under the age of 18. This assessment tool covers psychological, social and occupational functioning, and higher scores are associated with greater illness severity (Shaffer et al., 1983).

2.4. Statistical analysis

Statistical analyses were conducted using R software version 1.0.153 (https://www.R-project.org/). Descriptive analyses were reported as means (standard deviations) or absolute and relative frequencies. We divided participants into two groups: offspring PBD and non-offspring PBD. We used Pearson's chi-squared test ($\chi 2$) or Student t-tests to analyze demographic and clinical variables (comorbidity with ADHD, suicide attempts, psychosis, and rapid cycling which are associated with poor clinical outcomes) between these two groups. Clinical and demographic variables that were significantly different between the two groups were included in a logistic multivariate model. *P* values <0.05 were considered significant.

3. Results

Of the total 61 participants with PBD, 27 (44.3%) were offspring of bipolar parents, and 34 (55.7%) were offspring of controls (non-bipolar). No significant group differences were observed with respect to sex, age, ethnicity, IQ, or type of bipolar diagnosis.

3.1. Demographic and clinical variables

Table 1 presents group differences in demographic and clinical variables between PBD participants that are offspring of parents with BD and PBD offspring of non-BD parents, respectively. No statistically significant group differences were observed with respect to polarity of the first mood episode ($p = 0.70$), length of disease ($p = 0.23$), income ($p = 0.77$), CGI scores ($p = 0.74$), hospitalizations ($p = 0.59$), CGAS scores ($p = 0.31$), or mother's education level ($p = 0.41$). A statistically significant group difference was observed in comorbid ADHD diagnosis, such that offspring of parents with BD were significantly more likely to present with ADHD ($p = 0.02$), relative to offspring of parents without BD, with a large effect size ($X^2 = 4.9437$, $p = 0.0261$). Furthermore, PBD cases that were offspring of parents with BD showed a significantly

Table 1
Demographic and clinical variables.

Variables	Bipolar parents offspring (n = 27)	Non bipolar parents offspring (*n* = 34)	*t*-test or χ^2	*P*-value
Age[a]	11.44 ± 3.67	12.56 ± 3.04	$t = 1.269$	0.21
Sex[b]			$\chi^2 = 0.041$	0.83
Male	15 (55.6%)	18 (52.9%)		
Female	12 (44.4%)	16 (47.1%)		
Ethnicity[b]			$\chi^2 = 0.074$	0.78
Caucasian	19 (70.4%)	25 (73.5%)		
Non Caucasian	8 (29.6%)	9 (26.5%)		
IQ[a]	103.16 ± 12.92	98.455 ± 15.63	$t = -1.2187$	0.22
Polarity of first episode[b]			$\chi^2 = 0.710$	0.70
Depressive	17 (63%)	18 (53%)		
Mixed	5 (18.5%)	7 (20.6%)		
Mania	17 (63%)	9 (26.4%)		
Length of disease[a]	2.74 ± 3.02	1.97 ± 1.50	$t = -1.210$	0.23
Income[a,c]	3.31 ± 2.71	3.13 ± 2.17	$t = -0.288$	0.77
CGI [a]	3.55 ± 1.18	3.67 ± 1.64	$t = 0.332$	0.74
Hospitalization[b]			$\chi^2 = 0.289$	0.59
Yes	8 (29.6%)	8 (23.5%)		
No	19 (70.4%)	26 (76.5%)		
CGAS[a]	60.81 ± 18.86	56.44 ± 13.70	$t = -1.016$	0.31
Years of study mother[a]	10.26 ± 4.42	9.37 ± 3.86	$t = -0.820$	0.41
ADHD [b]			$\chi^2 = 4.9437$	0.02
Yes	21 (77.8%)	17 (50%)		
No	6 (22.2%)	17 (50%)		
Symptoms Onset [a]	5.81 ± 2.86	7.97 ± 3.59	$t = 2.603$	0.01
Rapid Cycling [b]			$\chi^2 = 2.249$	0.13
Yes	13 (48%)	10 (29.4%)		
No	14 (52%)	24 (70.6%)		
Lifetime psychosis [b]			$\chi^2 = 0.052$	0.81
Yes	8 (29,6%)	11 (32.3%)		
No	19 (70,4%)	23 (67.6%)		
Suicide Attempt [b]			$\chi^2 = 4.172$	0.65
No info	1 (3%)	2 (5.9%)		
Not at all	2 (7.4)	1 (3%)		
Slight	0 (0%)	1 (3%)		
Mild	6 (22.2%)	3 (9.4%)		

Abbreviations: IQ (coeffcient of intelligence), BD (bipolar disorder), NOS (not otherwise specified), CGI (clinical global impression), CGAS (children global assesment scale), ADHD (Attention deficit and hiperactivity disorder.

[a] Student *t*-test.

[b] χ^2 test.

earlier symptom onset ($p = 0.01$, $t = 2.603$), relative to PBD cases that were not offspring of parents with BD. No other significant differences were observed between groups.

Table 2 shows the results of the multivariate analysis. PBD offspring of BD parents showed an odds ratio (OR) of 3.5 (95% CI 1.13–10.83, $p = 0.02$) in ADHD comorbidity within the multivariate model. Moreover, PBD offspring of BD parents showed an OR of 2.23 of presenting with a rapid cycling course of illness.

Table 2
Logistic multivariate regression for the prevalence of ADHD in pediatric bipolar patients.

Variables	OR	95% CI	*P*-value
ADHD	3.5	(1.13–10.83)	0.02
Rapid Cycling	2.23	(0.78–6.4)	0.13
Lifetime psychosis	0.88	(0.29–2.63)	0.81

Abbreviations: ADHD (Attention deficit and hiperactivity disorder).

4. Discussion

To our knowledge, this is the first study to compare PBD offspring and PBD non-offspring specifically regarding clinical presentation. Our primary finding was that BD offspring show an increased prevalence of ADHD when compared to non-offspring. This is in line with previous literature, showing that ADHD is more common among offspring of parents with BD (Larsson et al., 2013) and that unaffected siblings of ADHD patients show an increased propensity for developing unipolar depression or bipolar disorder (Wei et al., 2018). Similarly, unaffected siblings of ADHD patients show a higher prevalence of developing bipolar disorder (Wei et al., 2018), and that prior diagnoses of ADHD and anxiety disorders are associated with a 30.46-fold increased risk of BD (Meier et al., 2018). Indeed, the prevalence of comorbid ADHD in BD patients is estimated between 9.5–28%, depending on study characteristics (van Hulzen et al., 2017).

Genetics studies have yielded controversial results regarding common genetic contributions for BD and ADHD. For instance, a previous study assessing known gene variants in six loci associated with BD, among 561 adult ADHD patients, found no strong evidence of shared risk variance between disorders (Landaas et al., 2011). However, a more recent and longitudinal genome-wide analysis, comprising 20,183 cases of ADHD and 7481 cases of BD, found multiple genes and pathways in common between ADHD, BD, and schizophrenia (Zhao et al., 2018).

Currently, it remains unclear whether ADHD symptomatology in a subset of BD patients represents a specific phenotype of BD with inattentive, hyperactivity and impulsivity dimensions, or true comorbidity between both disorders. For instance, bipolar patients with a history of ADHD symptoms show a 4.6 times greater prevalence of a rapid cycling course of illness, relative to those without a history of ADHD (Aedo et al., 2018). Additionally, higher rates of ADHD symptoms and neurodevelopmental abnormalities including learning disabilities and paranoid, schizoid or schizotypal traits were observed in offspring of parents who did not respond to lithium (Duffy et al., 2014). Furthermore, in a recent demographic and clinical analysis of 703 BD patients, higher inattentive scores, irritable temperament, male sex, lower depression scores, and a tendency toward mania and hypomania were more associated with comorbid ADHD (Pinna et al., 2019). However, it is also possible that misdiagnosis may also play a role in the apparent overlap between these disorders (Duffy, 2012), considering the substantial symptom overlap between disorders that we currently lack objective methods of diagnosis in psychiatry (Insel and Cuthbert, 2015).

There are important limitations in the present study, including a small sample size, cross-sectional study design, and the potential influence of recall bias during clinical interviews. However, the inclusion of patients irrespective of symptom severity, treatment and illness phase may allow for the broader generalizability of these results. Future longitudinal studies with adequate prospective follow-up will be required to confirm these findings and provide further information regarding the association of pediatric bipolar disorder and ADHD among offspring of BD patients.

Furthermore, while neuroanatomical changes have been found in comorbid ADHD and BD subjects, relative to ADHD subjects alone (Biederman et al., 2008), no studies thus far have assessed neuroanatomical alterations or differences in neural networks between pediatric ADHD, pediatric BD, and patients with both disorders. Importantly, there is also a lack of pediatric cohort studies assessing genetic or epigenetic differences between PBD, pediatric ADHD, and combined presentations. Future studies should focus on combined cohorts that comprise both offspring and non-offspring of BD patients, in order to help elucidate whether this comorbidity may reflect a phenotype of BD with a more severe clinical trajectory. Additionally, powerful multivariate techniques from the field of machine learning should consider ADHD comorbidity to build more monolithic subgroups of patients with

bipolar disorder (Librenza-Garcia et al., 2017; Passos et al., 2016b).

In summary, PBD offspring of BD patients showed a greater prevalence of ADHD symptomatology in the studied sample. Given these findings, we hypothesize that the combined clinical presentation of both disorders reflects a phenotype of BD with a more pernicious course of illness, although this will need to be confirmed in prospective studies.

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Declaration of Competing Interest

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