CLINICAL SCIENCE

Lifetime psychopathology among the offspring of Bipolar I parents

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BACKGROUND: Recent studies have demonstrated high rates of psychopathology in the offspring of parents with bipolar disorder. The aim of this study was to identify psychiatric diagnoses in a sample of children of bipolar parents.

METHOD: This case series comprised 35 children and adolescents aged 6 to 17 years, with a mean age of 12.5 ± 2.9 years (20 males and 15 females), who had at least one parent with bipolar disorder type I. The subjects were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS-PL). Family psychiatric history and demographics were also evaluated.

RESULTS: Of the offspring studied, 71.4% had a lifetime diagnosis of at least one psychiatric disorder (28.6% with a mood disorder, 40% with a disruptive behavior disorder and 20% with an anxiety disorder). Pure mood disorders (11.4%) occurred less frequently than mood disorders comorbid with attention deficit hyperactivity disorder (17.1%). Psychopathology was commonly reported in second-degree relatives of the offspring of parents with bipolar disorder (71.4%).

CONCLUSIONS: Our results support previous findings of an increased risk for developing psychopathology, predominantly mood and disruptive disorders, in the offspring of bipolar individuals. Prospective studies with larger samples are needed to confirm and expand these results.

KEYWORDS: Bipolar Disorder; Offspring; Psychopathology; Child; Adolescent.

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INTRODUCTION

Bipolar disorder (BD) in children and adolescents has long been associated with considerable global impairment and varied symptomatology.[1-4] Furthermore, it has a high familial loading,[5,6] and there is considerable evidence of its heritability.[7,8]

Early-onset BD was increasingly diagnosed over the past decade;[9] however, it remains a controversial diagnosis and a highly debated topic in child psychiatry. This controversy is primarily due to the high rates of comorbidity and overlap between BD and other psychiatric disorders commonly found in this age bracket.[10,11] For instance, chronic irritability is a symptom of a variety of childhood psychiatric disorders, including BD, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and conduct disorder (CD).[12] This overlap and lack of specificity of symptoms can interfere with experts' final diagnostic decisions.[13] In an attempt to overcome this diagnostic dilemma, some researchers have recommended that the cardinal symptoms of mania (elated mood or grandiosity) should be mandatory for a BD diagnosis in children.[14] In addition, the low prevalence rates of BD in children and adolescents around the world[15,16] are not compatible with the high rates found in clinical samples in the United States[17] and Brazil.[18] This discrepancy[19] is probably related to the current difficulties with diagnosing BD in children.

Retrospective studies that have assessed adults with BD have demonstrated an early age of onset of the disease.[20] Prodromal symptoms are identifiable in bipolar patients 9 to 12 years before their confirmed diagnoses.[21] Perlis et al.[22] identified an early onset of mood symptoms in 37.6% of their sample and an extremely early onset (e.g., before 13 years of age) in 27.7% of their sample. Henin et al.[23] reported elevated rates of childhood disruptive behavior disorders and anxiety

disorders in adult patients with BD (64%, compared to 15% in a control group without unipolar or bipolar mood disorders). In a review article, Conus et al.[24] described findings from different studies that indicated the presence of a bipolar prodromal phase characterized by mood swings, disturbed sleep, irritability and reduced functioning.

To ascertain the initial symptomatology of BD, assess early interventions and prevention measures and elucidate risk and protective factors, it is useful to evaluate BD prodromes. One way to achieve this goal is to study a population at high risk of developing BD. The offspring of bipolar parents are at high risk for different types of psychopathology, including BD. According to a meta-analysis, the offspring of bipolar parents are 4.0 times more likely to suffer from a mood disorder and 2.7 times more likely to suffer from any mental disorder than the children of healthy parents.[25] Moreover, many other studies with diverse designs have reported high rates of psychopathology, particularly mood and disruptive behavior disorders, in the offspring of bipolar parents.[26-32]

We evaluated the child and adolescent offspring of bipolar parents to further examine the presence of psychopathology in this population. Lifetime DSM-IV diagnoses, degree of functional impairment and severity of mood symptoms were examined, as were demographic characteristics and family psychiatric history.

METHODS

Subjects

The sample included 35 children and adolescents between 6 and 17 years of age who had at least one parent with DSM-IV BD type I. This broad age range, which included older children, was favorable to the identification of psychiatric disorders among the offspring of Bipolar I parents. The parents and their offspring were recruited from advertisements in the community and from the outpatient clinics at the University of Texas Health Science Center at San Antonio (n = 30) and at the Center for Excellence in Research and Treatment of Bipolar Disorder at the University of North Carolina at Chapel Hill (n = 5), where a number of the parents were already enrolled in other studies. In all families, the bipolar parent who was the informant in this study was an outpatient at the time of enrollment and was euthymic at the time of the assessments. Information about the noninformant parent was obtained from their bipolar partner.

Exclusion criteria for offspring included the presence of neurological disorders, history of head injury with loss of consciousness a family history of hereditary neurologic disorders or any current, serious medical problems.

Instruments and Procedures

This study was approved by the University of Texas at San Antonio and the University of North Carolina at Chapel Hill Institutional Review Boards. All offspring provided written assent, and the parents or legal guardians provided written consent prior to participation. The offspring were diagnostically evaluated using the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS-PL).[33] The Structured Clinical Interview for DSM-IV-TR SCID[34] was used to assess the lifetime history of psychiatric disorders for all bipolar parents and to confirm their diagnoses. To ascertain the psychiatric family history, a family history form that comprised questions about psychiatric problems in first- and second-degree relatives was used to guide direct interviews with the bipolar parent. To gather information about the participating children, the subject and his or her bipolar parent, most often the mother, were interviewed separately by trained psychiatrists with experience interviewing either children or adults. The interviewers were aware of the subjects' status as offspring of bipolar parents. The interview material was reviewed and discussed by the research team, and the final diagnoses were made during a consensus conference utilizing the DSM-IV criteria. In addition, the subjects and their parents completed the Children's Depression Rating Scale-Revised (CDRS-R)[35] and the Young Mania Rating Scale (YMRS)[36] to rate the severity of depressive and manic symptoms, respectively. Clinical depression was identified by CDRS-R scores above 40, and mania was identified by YMRS scores above 12. Overall impairment was measured using the Children's Global Assessment Scale (CGAS).[37] Socioeconomic status was assessed using the Hollingshead Four-Factor Index of Social Status.[38] All subjects received monetary compensation for their participation in the study.

RESULTS

The sample consisted of 35 child and adolescent offspring from 26 nuclear families with at least one parent (in most cases [82.9%], the mother) with BD type I (Table 1). Of these 35 participants, 14 were siblings, two were half-siblings and 19 were unrelated. The subjects had a mean $\pm$ S.D. age of 12.5 $\pm$ 2.9 years, range six to 17 years. Fifteen (42.9%) were girls, and 20 (57.1%) were boys. In terms of ethnicity, 57.1% were Caucasian, 34.3% were Hispanic and 8.6% were African-American. The three ethnic groups were evenly distributed among the groups affected and unaffected by psychiatric disorders. The mean $\pm$ S.D. for years of education in the offspring group was 6.4 $\pm$ 3.0. The mean Hollingshead socioeconomic status was 43.1 $\pm$ 15.3, which falls within social class III. This class includes parents who may be small business owners or technicians and have completed some college.

Psychopathology in BD Offspring

As shown in Table 1, 25 of the 35 participants (71.4%) met the DSM-IV criteria for at least one psychiatric disorder. Of these 25 children, three (8.6%) were diagnosed with BD; two met the DSM-IV criteria for BD type I, and one was diagnosed with BD not otherwise specified (NOS). Seven children (20.0%) received a diagnosis of major depressive disorder. The remaining 15 (42.9%) received other Axis 1 diagnoses, as follows: four were diagnosed with ADHD, mostly combined type; four with ADHD plus ODD; three with generalized anxiety disorder alone; two with enuresis; one with an adjustment disorder; and one with anxiety disorder NOS. Ten (28.6%) of the children and adolescents did not receive any psychiatric diagnosis.

Comorbidity with ADHD was present in six (60.0%) of the ten children with mood disorders, including those with BD. In all six of these subjects, ADHD onset occurred at least one year before the onset of mood disorders. Comorbid anxiety disorders were found in three of these ten children (30.0%), comorbid ODD in one child (10.0%),

Table 1 - Demographics, clinical characteristics, and lifetime psychiatric diagnoses of the offspring (N = 35).

Child variables	Mean ± SD	N (%)
DEMOGRAPHICS		
Female		15 (42.9)
Age, years	12.5 ± 2.9	
Years of schooling	6.4 ± 3.0	
Hollingshead SES	43.1 ± 15.3	
CLINICAL CHARACTERISTICS		
CGAS	75.5 ± 14.7	
CDRS-R	23.8 ± 8.7	
YMRS	3.3 ± 4.1	
On psychiatric medication		10 (28.6)
Psychiatric hospitalization		5 (14.3)
LIFETIME PSYCHIATRIC DIAGNOSES*		
Bipolar disorder type I		2 (5.8)
Bipolar disorder NOS		1 (2.9)
Major depressive disorder		7 (20.0)
Generalized anxiety disorder		5 (14.3)
Separation anxiety disorder		1 (2.9)
Obsessive compulsive disorder		1 (2.9)
Anxiety disorder NOS		1 (2.9)
Oppositional defiant disorder		5 (14.3)
Attention deficit hyperactivity disorder		14 (40.0)
Conduct disorder		1 (2.9)
Adjustment disorder		1 (2.9)
Enuresis		3 (8.6)
No psychiatric disorder		10 (28.6)

Abbreviations: SD: Standard deviation; SES: Socioeconomic status; CGAS: Clinical global assessment scale; CDRS-R: Children's Depression Rating Scale - Revised; YMRS: Young Mania Rating Scale; NOS: Not otherwise specified.
*Some children had more than one diagnosis.

comorbid CD in one child (10.0%), and comorbid enuresis in one child (10.0%).

The mean age at onset of mood symptoms among the subjects with bipolar and major depressive disorder was 8.6 ± 2.8 years. Specifically, children with BD type I (n = 2) developed their first mood symptoms at five or six years of age, and the child with BD-NOS experienced an onset of mood symptoms at eight years of age. Moreover, both children with BD type I had episodic courses, exhibiting elated moods during manic episodes, and one had a prior history of psychiatric hospitalization. The BD-NOS subject had short phases (lasting less than four days) of moderately elevated mood that occurred with other manic symptoms; however, this subject did not meet all the DSM-IV diagnostic criteria for BD type I or II.

Of the 35 subjects, three had CDRS-R scores above 40, and just one scored above 12 on the YMRS. The mean CGAS score for the entire sample was 75.5 ± 14.7. The offspring with psychiatric disorders had a mean CGAS score of 70.2 ± 13.9; the mood disorders group had the lowest mean score (64.5 ± 17.5), whereas the unaffected participants had the highest mean score (88.7 ± 5.2) ($p<0.001$).

Ten participants were taking psychiatric medications at the time of assessment (three of those were diagnosed with BD, two with major depression, four with ADHD, and one with enuresis). The medications used included atypical antipsychotics, antidepressants, psychostimulants and an anticholinergic drug.

Family Characteristics

Sixty-three percent of the families were single-parent or blended families; in these cases, limited contact and a poor relationship between the children and the absent parent were often reported. One child resided with a guardian at the time of the study. Generally speaking, most families had a significant psychiatric history, with more than one member in addition to the bipolar parent who suffered from a mental illness. Among the 35 offspring, 25 (71.4%) had second-degree relatives with a history of psychiatric disorders. Of these 25, 21 had second-degree relatives with a mood disorder, nine with alcohol or other drug dependence, six with anxiety disorders, and two with schizophrenia (Table 2).

The most common comorbidity among the bipolar parents was an anxiety disorder. Anxiety disorders, most commonly posttraumatic stress disorder (PTSD), were present in almost 40% of the bipolar parents. Alcohol and cannabis dependence were present in only two parents, and in both cases, partial remission was sustained.

The noninformant parents were not formally assessed, but in most cases, they had a history of a psychiatric disorder, according to information provided by their bipolar partner. Ten (28.6%) were reported to have a mood disorder, mostly major depressive disorder, and one had a probable BD comorbid with drug dependence. Five (14.3%) were reported to have alcohol or other drug dependence, in one case comorbid with an anxiety disorder. One (2.9%) had schizophrenia. The psychiatric history of three (8.6%) was unknown, and the remaining 16 (45.7%) had no history of psychiatric disorder.

DISCUSSION

The present study is consistent with previous works that have demonstrated high rates of psychiatric disorders in children and adolescents with at least one parent diagnosed with BD type I. Among these offspring, 71% received at least one psychiatric diagnosis, which is similar to the rates reported in prior bipolar offspring studies (72% and 78%)[31,39] but is slightly higher than the rate found in a meta-analysis (52%).[25]

The lifetime prevalence of depression has been reported to increase from childhood to adolescence[40] and also to increase during adolescence.[41] In the general population, the lifetime prevalence of major depression among adolescents ranges from 12% to 20%.[41-43] According to a meta-analysis that included epidemiological studies of children and adolescents with formal psychiatric diagnoses of depressive psychiatric disorders, rates of depression were higher in adolescents 13 to 18 years old than in children under 13.[44] The prevalence of depressive disorder in our sample (which included both children and adolescents) was higher than these estimates. This finding indicates that the offspring of bipolar parents are at serious risk of being affected by mood disorders. Moreover, data from existing longitudinal studies of the offspring of bipolar parents have demonstrated that the first manic phase is generally preceded by depressive symptoms.[45-47] Thus, these results make it plausible to hypothesize that some of the subjects in the present study who presented with major depressive disorders will meet the criteria for BD in the future.

In the present study, ADHD and anxiety disorders were observed in significant proportions among the offspring of

bipolar parents, confirming the findings of previous studies.[27-30] In the studied sample, ADHD and anxiety disorders were also highly comorbid with mood disorders. These findings are in agreement with prior research conducted on the offspring of bipolar parents.[27,29] The high levels of ADHD comorbid with depression distinguish the children of bipolar parents from the general population of children and adolescents. Indeed, a review of population-based studies involving this age range showed that the highest levels of comorbidity were between depression and anxiety disorders and between ADHD and ODD/CD.[48] The high rates of comorbidity with ADHD presented by bipolar youth[49] suggest that ADHD in children of bipolar parents may be a marker of increased vulnerability to BD.

Furthermore, among the subjects affected by comorbid mood disorders and ADHD, ADHD onset occurred before the onset of mood symptoms in 100% of the cases, and the same was true for just over 50% of participants diagnosed with anxiety disorders. Hence, some disruptive behaviors and even anxiety observed in a high-risk sample could be cautiously interpreted as potential precursors of future mood disorders,[50] especially BD, as has been previously suggested.[29,51-54] The exact nature of the association between BD and disruptive or anxiety disorders in children and adolescents is not yet completely understood. Nevertheless, considering the sequential chronological onset of these disorders in at-risk children, it is important to recognize the possibility of a BD diagnosis at some point in time.

Regarding overall functioning, the subjects in the present study had fairly high levels of global functioning, as measured by the CGAS, despite their high rates of psychopathology. Even the lowest-functioning group, those with mood disorders, received a mean CGAS score above 61, which indicates a relatively good level of function with some difficulties in a single area. Several prevalence studies of psychiatric disorders[16,55,56] have reported the coexistence of a DSM-III-R or DSM-IV diagnosis and good global functioning in children and adolescents. This unexpectedly good level of functioning in the present sample might be a result of easy access to mental health services, the increased availability of more effective treatments (including medicines and psychosocial interventions) and early diagnosis.

Additionally, most subjects in this study had multiple first- and second-degree relatives with histories of mental illness, particularly mood disorders and alcohol or other drug dependence, so a high familial loading was present in our sample. The noninformant parents were often reported to be suffering from psychiatric disorders as well; almost 30% were reported to have a mood disorder, which supports the assumption of the high heritability of BD.

Environmental risk factors mentioned in both the meta-analysis of children of parents with BD[25] and in a review of studies of children of bipolar parents[57] were also present in this sample. In other words, the parents' divorce rates were above 60% and, consequently, the majority of families who took part in this study were single-parent or blended families. The relationships among family members were described as unsupportive, suggesting the presence of poor parenting skills, a factor known to negatively affect children's mental health.

The high rates of mental disorders among the participants' relatives, the high rate of comorbid PTSD in the proband parents and the elevated number of environmental risk factors mentioned suggest that these families might be quite vulnerable and more dysfunctional than the families included in other high-risk studies.[58] This fact may have predisposed the studied offspring to a relatively early onset of mood symptoms.

Table 2 - Family psychiatric histories of the offspring of bipolar parents (N = 35).

Psychiatric disorders*	Noninformant parent** N (%)	Second-degree relatives N (%)
Mood disorders	10 (28.6)	21 (60.0)
Alcohol/drug dependence	6 (17.1)	9 (25.7)
Schizophrenia	1 (2.9)	2 (5.8)
Anxiety disorders	1 (2.9)	6 (17.1)
No psychiatric disorders	16 (45.7)	10 (28.6)
No information	3 (8.6)	0 (0.0)

*Comorbidities are possible.
**Spouse of the bipolar informant parent.

Some limitations of the present study must be taken into account. The study design was a cross-sectional case series with a limited sample size, and no control group was available for comparison. The inclusion of families already engaged in imaging studies at the same center might have caused a selection bias by including subjects that were not representative of the offspring of bipolar parents in general. In addition, not all of the biological children of the bipolar informant parents participated in the study. Despite these limitations, our study was in line with recent literature, revealing that the offspring of parents diagnosed with BD are a high-risk population that deserves special attention to detect possible early symptoms of psychiatric abnormalities. Moreover, this study indicates that more studies, particularly longitudinal ones, are needed in this field.

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