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Original Article

Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder

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Objectives: The primary purpose of this study was to describe the clinical presentation of bipolar I disorder (BP-I) as it occurs in children and adolescents and to assess whether the manifestations of BP-I were similar in both age groups.

Method: Ninety youths between the ages of 5 and 17 years meeting full diagnostic symptom criteria for BP-I were included in this study. The diagnosis of BP-I was established for these youths based on the results of a semi-structured diagnostic interview and a clinical assessment by a child and adolescent psychiatrist. The course of a subset of these youngsters' illnesses was assessed using the Life Charting Method (LCM). Data regarding the clinical presentation, longitudinal history, psychiatric co-morbidities and parental psychopathology were also obtained.

Results: The clinical presentation of BP-I was similar in children and adolescents. Youths meeting diagnostic criteria for BP-I developed an average of approximately 5.8 of the 7 symptoms of mania during periods of elevated or irritable mood. BP-I was found to be a cyclic disorder characterized by high rates of rapid cycling (50%) with almost no inter-episode recovery. Almost 75% of these subjects also met diagnostic symptom criteria for a disruptive behavior disorder. High rates of mood disorders were found in fathers.

Conclusions: These data suggest that the presentation of juvenile BP-I is a cyclic and valid clinical condition with manifestations on a continuum with the later-onset forms of this illness.

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The existence of bipolar disorder in juveniles has been noted for over a century (1). However, the data suggest that the clinical manifestations of the disorder differ in children and adolescents. When compared to adults, accurate identification of this condition in youths may be difficult (2–5).

There are few prospective studies that have directly compared the clinical presentation of bipolar disorder in different age groups. In one such study, it has been reported that adolescents hospitalized for bipolar disorder experience mixed states more frequently and experience psychosis less frequently than do adults who are hospitalized with this same syndrome (6). Similarly, it has also been suggested that patients who develop a bipolar spectrum disorder during childhood or early adolescence have a different course of illness when compared to patients who develop bipolar disorder later in life (7–9). Whereas the adult-onset forms of bipolar-spectrum illnesses are sometimes characterized by distinct, lengthy mood states and inter-episode recovery, initial data suggest that children and young adolescents who have bipolar spectrum disorders suffer from an illness characterized by brief mood episodes, rapid cycling, mixed states and an absence of inter-episode recovery (7, 8). Unfortunately, there is a paucity of systematic data to either confirm or refute these preliminary observations.

It has also been asserted that some children who suffer from mania may suffer from an affective disorder that is not characterized either by mood cycling or distinct mood episodes. Some have suggested that children who meet diagnostic criteria for mania may be chronically irritable and dysphoric (9). Since the key hallmarks of bipolar disorder, as currently defined, include discrete mood episodes, others have questioned whether these pervasively irritable youths suffer from bipolar disorder (10).

In order to establish the diagnostic validity for a psychiatric illness, it has been contended that a condition must not only be described and delineated from other conditions, but that data from family studies, longitudinal examination and laboratory testing be considered (11). Although laboratory testing is not available to definitively confirm or refute the diagnosis of bipolar disorder, there is some evidence from brain imaging studies to suggest that differences in cerebral morphology exist when youths with bipolar spectrum disorder are compared to normal controls (12–14). Youths with bipolar disorder have also been reported to have high rates of mood disorders among family members (15–17). In addition, it has also been noted that young people with bipolar disorders suffer from greater degrees of mood symptomatology that differentiate these patients from those with disruptive behavior disorders or controls (18–21).

A careful description of the clinical presentation and longitudinal course of juveniles with bipolar I disorder (BP-I) would provide clinicians with information that might facilitate its accurate identification. The primary purpose of this study was to describe the clinical picture of BP-I in children and adolescents.

Methods

Subjects

In order to be enrolled in this study, children and adolescents had to be outpatients between the ages of 5 and 17 years (inclusive). Youths with clinical evidence of a pervasive developmental disorder or mental retardation were not included in this study in order to avoid the possible confounds of these co-morbidities. All subjects received a clinical assessment by a child and adolescent psychiatrist and a semi-structured diagnostic interview. In order to be enrolled in this study, individuals had to meet full diagnostic criteria for BP-I (including 1-week duration and symptom severity criteria for manic episodes) after both modes of assessment. DSM-IV criteria for BP-I were not modified for this study. As part of this protocol, information about the subjects' educational history and current living circumstances was obtained.

Subjects were recruited for this protocol from a clinical research center (CRC) that is dedicated to the study of juvenile bipolar disorders. The CRC is located within a university-based division of child and adolescent psychiatry. Telephone referrals for participation in CRC studies come from within the division or from referrals made directly to the CRC. After a telephone screen, potential subjects are then scheduled to meet with a research assistant for a semi-structured diagnostic interview.

The semi-structured diagnostic interview the youths received was either the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (K-SADS-E) or the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime-Version (K-SADS-PL) (22). Both the K-SADS-E and the K-SADS-PL assess the presence or absence of previous or current psychiatric symptomatology based upon information provided by both the subject and the subject's guardian. In addition, these semi-structured interviews gather information regarding the time course of a patient's illness as well as the presence or absence of course modifiers for bipolar disorder. The K-SADS-E was initially employed. However, as the K-SADS-PL has modules that can be omitted based on informant response, the later patients in this study were interviewed with the K-SADS-PL in order to improve subject acceptability. Physicians, master's-level or bachelor's-level interviewers administered the K-SADS interviews. Inter-rater reliability on the K-SADS was assessed with the kappa statistic. Before leading a K-SADS interview, all research assistant raters demonstrated adequate inter-rater reliability (kappa ≥ 0.85) and diagnostic agreement based on the results of five K-SADS interviews. Subsequently, inter-rater reliability was maintained (kappa ≥ 0.85) by having joint assessments at approximately every tenth interview.

As part of the physician's clinical assessment, both the young person in question and his/her guardian(s) were interviewed. These interviews typically lasted approximately 90 min. The study physicians also considered all available clinical information before establishing a diagnosis of BP-I for the patients.

The University Hospitals of Cleveland Institutional Review Board for Human Investigation approved the procedures of this study. After

complete description of the study to the subjects and their guardians, written informed consent from the guardians and assent from the subjects were obtained. All subjects meeting enrollment criteria were included in this study.

Symptomatology of mania and psychiatric co-morbidity

In order for a symptom of mania to be considered present during the patient's course of illness, the symptom had to be rated as being of moderate to severe magnitude on the present episode section of the KSADS-E, or to be considered definitively present either on the past episode section of the K-SADS-E or on the past or present episode sections of the K-SADS-PL. In addition, for a symptom of mania to be considered present, that symptom needed to either become manifest or become exacerbated during episodes of elevated, expansive or irritable mood. For a patient to receive the diagnosis of one or more co-morbid psychiatric disorders, a patient needed to meet full diagnostic symptom criteria for each co-morbid diagnosis during identified periods of neutral mood according to the semi-structured diagnostic interview.

Family history

Attempts were made to obtain diagnostic assessments for all biological parents of all youths who participated in this study. When parents could be interviewed directly, lifetime diagnoses were obtained using the Schedule for Affective Disorders and Schizophrenia (SADS) based upon DSM-IV criteria (23). If a parent could not be interviewed directly, either the Family History Research Diagnostic Criteria (FH-RDC) interview (24) was administered to an informant (typically a parent) regarding the unavailable parent or records from the adult Mood Disorders Program at this institution (JRC, Director) were obtained.

Longitudinal course

Parents were requested to describe the longitudinal course of the youths' illnesses with the Life Charting Method (LCM) (25). After being instructed on the completion of the LCM, parents were then asked to complete prospective and/or retrospective life charting. There are some preliminary data to suggest that the LCM may have utility in the longitudinal assessment of young people with bipolar disorder (26).

Statistical analyses

For purposes of analysis, the subjects were divided into two groups. Subjects between the ages of 5 and 11 years (inclusive) were considered children. Those between the ages of 12 and 17 years were considered adolescents. Nominal data were compared to the chi-squared test or Fisher's exact test, as appropriate. Continuous data were initially assessed for normal distribution with the Lilliefors and Kolmogorov–Smirnov test. Since the majority of variables did not meet this stringent standard for normal distribution, the Mann–Whitney U-test was applied to all continuous variables. The alpha level for statistical significance was set at $p \leq 0.05$. All statistical tests were two-tailed. Data analyses were performed with SPSS (27). Means are presented with their standard deviations in parentheses unless otherwise noted.

Results

Clinical description

Ninety subjects were enrolled in this study. Forty-seven percent ($n = 42$) of the patients were assessed using the K-SADS-E and the other subjects were assessed using the K-SADS-PL. Demographic information about these youths can be found in Table 1.

Approximately twice as many males than females were present in this cohort. The proportion

Table 1. Demographic data for 90 youths with bipolar I disorder

	Children	Adolescents	All subjects
Number of youths	56	34	90
Mean age in years[a]	8.5 (1.9)	14.5 (1.7)	10.8 (3.5)
Number of males[b]	42 (75.0%)	22 (64.7%)	64 (71.1%)
Age at first manic episode (years)[a]	5.0 (2.6)	9.5 (4.4)	6.7 (4.0)
Currently living with both biological parents[b]	28 (50.0%)	11 (32.4%)	39 (43.3%)
Ever in special education[b]	15 (26.8%)	7 (20.6%)	22 (24.4%)
Past psychiatric hospitalization[b]	14 (25.0%)	14 (41.2%)	28 (31.1%)

[a]Presented as mean (standard deviation).
[b]Presented as number of subjects (percentage).

Table 2. Symptoms developing during mania in 90 youths with bipolar I disorder

Symptom[a]	Children (n = 56)	Adolescents (n = 34)	Total (n = 90)	p[b]
Grandiosity	48 (85.7%)	27 (79.4%)	75 (83.3%)	0.437
Decreased need for sleep	39 (69.6%)	26 (76.5%)	65 (72.2%)	0.483
More talkative	47 (83.9%)	26 (76.5%)	73 (81.1%)	0.381
Racing thoughts	49 (87.5%)	30 (88.2%)	79 (87.8%)	1.00
Distractibility	46 (82.1%)	30 (88.2%)	76 (84.4%)	0.439
Increased goal-directed activity/agitation	43 (76.8%)	30 (88.2%)	73 (81.1%)	0.178
Poor judgment	51 (91.1%)	26 (76.5%)	77 (85.6%)	0.069

[a]Data presented as number present (percentage).
[b]p-values comparing differences in rates at which diagnostic criteria are present for each child and adolescent using the chi-squared or Fisher's exact test (both with df = 1), as appropriate.

of males and females in each age group was not significantly different ($\chi^2 = 1.09$, df = 1, $p = 0.296$). Not surprisingly, the first manic episode occurred at an earlier age in the children when compared to the adolescents ($Z = 4.68$, $p < 0.0005$).

Less than half of these patients lived with both of their biological parents (43.3%), with a similar proportion of patients of both age groups living with both parents ($\chi^2 = 2.68$, df = 1, $p = 0.101$). Approximately one in four patients ever received special education services. The proportion for both age groups was not different ($\chi^2 = 0.28$, df = 1, $p = 0.598$). As far as psychiatric hospitalizations are concerned, there was a trend for more adolescents to have received inpatient psychiatric care than children ($\chi^2 = 2.91$, df = 1, $p < 0.10$).

Over the course of their lifetime, the average total number of psychotropic medications that had been prescribed to these youths was 3.94 (3.42). The mean number of medications that had been prescribed to the children was 4.07 (3.93) and the mean number of medications that had been prescribed to the adolescents during their lifetime was 3.74 (2.40). At the time of assessment, the youths were on an average of 1.56 (1.35) psychotropic medications with the children on 1.50 (1.31) and the adolescents on 1.65 (1.43) agents. The total amount of medication exposures, lifetime and current, did not differ substantially between the two age groups ($Z = 0.529$, $p = 0.597$ and $Z = 0.449$, $p = 0.654$, respectively).

Manic symptomatology

The presence or absence of each of the diagnostic symptom criterion that developed during identified manic episodes was noted as part of the K-SADS interview. Data about the symptom criteria for mania are given in Table 2.

Of the seven symptoms of a manic episode, the average number of symptoms recorded as developing during manic episodes was 5.77 (1.39); for children it was 5.77 (1.32) and for adolescents it was 5.76 (1.52). These numbers did not differ from each other ($Z = 0.284$, $p = 0.777$).

Major depressive episodes were relatively common in these patients, with approximately half of these patients [46.7% (n = 42)] experiencing a major depressive episode at one point in time. A major depressive episode had occurred in 22 children (39.3%) and 20 adolescents (58.8%). The proportion of patients did not differ from each other ($\chi^2 = 3.25$, df = 1, $p = 0.072$).

Psychosis and longitudinal course modifiers

High rates of rapid cycling were noted in these ninety patients (Table 3). In addition, a 2-month inter-episode recovery was seen in only 5.9% of adolescents and not at all in children. Conversely, rates of mixed states and psychosis were relatively low in both children and adolescents.

Psychiatric co-morbidity

Most of these youths (83.9% of children, 76.5% of teenagers; 81.1% overall) met diagnostic criteria for a co-morbid psychiatric condition while euthymic (Table 4). The proportion of subjects meeting DSM-IV criteria for a co-morbid condition did not differ between the age groups ($\chi^2 = 0.77$, df = 1, $p = 0.381$). Disruptive behavior disorders were quite common. These conditions were noted in 74.4% of this cohort (76.8% of children and 70.6% of adolescents). Attention deficit/hyperactivity disorder (ADHD) was the most common co-morbidity. It was found in 70.0% of the youths (75.0% of children and 61.8% of adolescents). There were no differences in the rate at which ADHD occurred in the children when compared to the adolescents ($\chi^2 = 1.77$, df = 1, $p = 0.184$). Only two of the subjects (both children) with ADHD suffered from the hyperactive-impulsive subtype of this syndrome, and two (both children) met criteria for the pre-

dominantly inattentive subtype. Most patients suffered from the combined subtype of ADHD.

No children met DSM-IV criteria for a substance abuse disorder. However, 17.6% of teenagers (n = 6) met DSM-IV criteria for a substance abuse disorder. This difference was statistically significant (Fisher's exact test, df = 1; p = 0.002). The onset of bipolar disorder preceded the development of a substance abuse disorder in five out of six cases (83%).

Family history

Sixty (66.7%) youths had psychiatric data available for both parents (37 children, 23 adolescents). Of this cohort of 90, 12 had psychiatric data available for only 1 parent (10 children, 2 adolescents). In addition, 18 youths had psychiatric data available for neither parent (9 children, 9 adolescents). Overall, psychiatric assessments could be obtained for approximately 76.7% of the mothers of both the children and adolescents (80.4% and 70.6%, respectively). Of the 69 mothers assessed, 59 were evaluated using the SADS. Eight were assessed using the FH-RDC interview and 2 had been assessed clinically by one of the authors (JRC). Sixty-three of the fathers from this cohort of youths could be evaluated. Fathers of 39 children and 24 adolescents were assessed. However, the psychiatric symptomatology of less than half of these 63 fathers was assessed using the SADS (n = 29). Data regarding mood disorders in parents of youths with BP-I are summarized in Table 5. The subjects for whom parent data were available versus unavailable did not differ significantly in terms of demographics, number of present or lifetime prescriptions or rate of co-morbid diagnoses (all p-values > 0.05). The one possible exception was the rate of psychiatric hospitalizations, with children missing parent data having a slightly higher hospitalization rate ($\chi^2 = 4.01$, df = 1, p = 0.045).

Of the sixty subjects who had available family history data pertaining to both parents, 81.7% of them were found to have at least one parent who suffered from an identifiable mood disorder according to the SADS or the FH-RDC. The percentage of these children with at least one identified parent with a mood disorder was 81.1% (n = 30), and the percentage of adolescents with at least one parent identified as suffering from a mood disorder was 82.6% (n = 19). The proportion of youths with one identified parent with a mood disorder did not differ between the age groups (Fisher's exact test: df = 1, p = 1.00). Of the 12 subjects who had available family history data pertaining to only 1 parent, 8 of them were found to have had the one available parent suffer from a mood disorder (7/10 children, 1/2 adolescents).

Longitudinal course/life charting

Prospective and/or retrospective life charting could be obtained for 57 of these 90 subjects (32 children and 25 adolescents). There were no significant differences between youths 'with' versus 'without' life charting data available (all p-values > 0.04, with almost all p-values substantially greater than 0.10). The parent/guardians of all adolescents described a cyclic mood disorder characterized by periods of elevated mood alternating with periods of either euthymia or depression. The guardians of all children, except one, also longitudinally charted a condition in which cyclic changes in mood occur. The parent of only one child (a 5-year-old male) reported a condition characterized by chronic elevation in mood. A fuller description of these data is beyond the scope of this paper.

Discussion

These results suggest that the manifestations of BP-I are generally alike in both children and adolescents. As suggested in a smaller study (7), juveniles with BP-I were found to have high rates of rapid cycling without inter-episode recovery.

In addition, although there were low rates of inter-episode recovery, distinct periods of euthymia were able to be identified in order to assess for

Table 3. Symptomatic and longitudinal course modifiers in 90 youths with bipolar I disorder[a]

Modifier	Children (n = 56)	Adolescents (n = 34)	Total (n = 90)	p[b]
Mixed states	11 (19.6%)	7 (20.6%)	18 (20.0%)	0.913
Rapid cycling	26 (46.4%)	19 (55.9%)	45 (50.0%)	0.384
Inter-episode recovery[c]	0 (0.0%)	2 (5.9%)	2 (2.2%)	0.140
Psychosis	10 (17.9%)	5 (14.7%)	15 (16.7%)	0.697

[a]Data presented as number (percentage) in which the modifier was present.
[b]p-values comparing differences in rates at which diagnostic criteria are present for each child and adolescent using the chi-squared or Fisher's exact test (both with df = 1), as appropriate.
[c]Inter-episode recovery was considered to be present if there was a 2-month period of affective symptom remission.

Table 4. Rates of psychiatric co-morbidity in 90 youths with bipolar I disorder[a]

Diagnosis	Children (n = 56)	Adolescents (n = 34)	Total (n = 90)	p[b]
ADHD-combined	37 (66.1%)	20 (58.8%)	57 (63.3%)	0.489
ADHD-hyper/impulsive	2 (3.6%)	0 (0.0%)	2 (2.2%)	0.525
ADHD-inattentive	2 (3.6%)	0 (0.0%)	2 (2.2%)	0.525
ADHD-NOS	1 (1.8%)	1 (2.9%)	2 (2.2%)	1.00
OpDD	26 (46.4%)	16 (47.1%)	42 (46.7%)	0.954
CD	10 (17.9%)	5 (14.7%)	15 (16.7%)	0.697
Any anxiety disorder	7 (12.5%)	6 (17.6%)	13 (14.4%)	0.546

[a]Data presented as number (percentage).
[b]p-values comparing differences in rates at which diagnostic criteria are present for each child and adolescent using the chi-squared or Fisher's exact test (both with df = 1), as appropriate.
ADHD-combined = attention deficit/hyperactivity disorder, combined type; ADHD-hyper/impulsive = attention deficit/hyperactivity disorder, hyperactive-impulsive type; ADHD-inattentive = attention deficit/hyperactivity disorder, inattentive type; ADHD-NOS = attention deficit/hyperactivity disorder, not otherwise specified; OpDD = oppositional defiant disorder; CD = conduct disorder.

psychiatric co-morbidity. It appears to us that, not only are the periods of euthymia not sustained, but they seem to be reasonably brief. Relatively low rates of psychosis were noted. This may be due to the fact that this was an outpatient study. Although less than 25% of adults with bipolar disorder have reported suffering from the rapid cycling variant of this condition (28), recent data from the Stanley Foundation Bipolar Network show a 52% incidence of rapid cycling (29). Approximately half of the patients in this cohort appeared to have rapid cycling. Consistent with other reports, these data suggest the possibility that the rapid cycling variant of BP-I may be more common in young people than in adults (20, 30). This is particularly noteworthy since most adults with rapid cycling suffer from bipolar II disorder (28).

In this group of youths with BP-I, there were approximately twice as many males as females. Several prior studies of juvenile BP-I have also included more males than females (9, 20, 31). Although BP-I appears to affect the genders equally during adulthood (32, 33), it is possible that juvenile BP-I may be more common in males.

During periods of mania, it appears as if young people with BP-I will manifest the same symptoms associated with mania in adults. In addition, like adults with bipolar disorder, relatives of these youths with BP-I had high rates of mood disorders (34).

When the parents of these subjects provided life charting data about the longitudinal course of their child's condition, distinct mood episodes were reported. The life charting data do not necessarily contradict the observation that youths with BP-I may be chronically and pervasively irritable (9). According to current nosology, periods of mania, hypomania or mixed states can be characterized by irritability. Similarly, youths may appear more irritable than sad during periods of depression. Finally, youths with BP-I may seem quite irritable even during periods of euthymia. Almost half of these youths were found to suffer from co-morbid oppositional defiant disorder (OpDD) during periods of relative euthymia. Youths with OpDD may easily lose their temper, may be quick to anger and are sometimes easily annoyed even though they are not suffering from a mood disorder (35). For these reasons, juveniles with BP-I may be viewed as being chronically irritable.

As reported in other cohorts, the youths with BP-I seen at this Center had high rates of co-morbid psychiatric illnesses, particularly the disruptive behavior disorders (15, 19, 36, 37). However, considering that high rates of co-morbid anxiety disorders have been described elsewhere for young people with bipolar disorder (2, 37), it was surprising to find that only a small number of the subjects described herein were noted as meeting full diagnostic criteria for an anxiety disorder. This is possibly due to the fact that these patients were only diagnosed as suffering from a co-morbid psychi-

Table 5. Family history data in youths with bipolar disorder[a]

Parent	Children	Adolescents	Total
Mother: bipolar spectrum[b]	13 (28.9%)	6 (25.0%)	19 (27.5%)
Mother: depression spectrum	17 (37.8%)	7 (29.2%)	24 (34.8%)
Father: bipolar spectrum	17 (43.6%)	10 (41.7%)	27 (42.9%)
Father: depression spectrum	6 (15.4%)	3 (12.5%)	9 (14.3%)

[a]Data presented as number (percentage). Data are available for 69 mothers of 45 children and 24 adolescents. Data are available for 63 fathers of 39 children and 24 adolescents.
[b]Bipolar spectrum – bipolar I disorder, bipolar 2 disorder, cyclothymia, or bipolar disorder not otherwise specified.

atric condition if they met symptom criteria for the condition during identified periods of euthymia. It has been previously recognized that symptoms of anxiety disorders are present during periods of both depression and mania/hypomania (38–40). For this reason, although youngsters with BP-I might manifest symptoms of anxiety disorders during mood episodes, these data suggest that the anxiety observed in many of these youths might dissipate as the abnormal mood states associated with BP-I resolve.

Approximately 20% of the subjects were found to suffer from mixed episodes. Higher rates of mixed states have been reported for juveniles with bipolar disorder (6, 9, 20, 30). Patients were only considered to have experienced a mixed episode if they not only met full symptom criteria for a mixed state, but also met the 1-week duration criteria. Data from this Center support the observation that youths with BP-I are sometimes quite dysphoric with high rates of depressive symptoms (41). Although both depressive symptomatology and manic symptomatology may be simultaneously present in young people with BP-I, thereby having a 'mixed' presentation, it may be that the majority of juveniles with BP-I do not meet full DSM-IV diagnostic symptom criteria for a mixed episode.

The strengths in the design of this study are as follows. The sample size is one of the largest in juveniles with bipolar illness. The diagnosis of BP-I in these youths was based on information provided by both the subjects and their guardians based on a clinical assessment and a semi-structured diagnostic interview. Additional evidence to support the diagnosis of BP-I was accurate in this cohort comes from the LCM and the family histories obtained from these youths' parents. Other work completed here corroborates the finding that youths diagnosed with BP-I at this Center suffer from a form of psychopathology that is distinct from other conditions (42, 43).

However, it is important to note that there are several shortcomings to this study. This was not an epidemiological study. Therefore, it is possible that the youths who were examined were not representative of youths with BP-I. Subsequent epidemiological studies might consider less selective cohorts. In addition, it is important to appreciate that there is evidence that BP-I may not be the most common form of bipolar spectrum disorders in young people (37). This work probably describes only the most profoundly affected outpatient youths with bipolar spectrum disorders. In addition, the average age at onset for these adolescent patients was 9.5 years. Therefore, this study does not fully consider the symptomatology of later adolescent-onset bipolar disorder. This may explain why substantial differences between the two age groups were not found.

Another limitation of this study is the use of standard K-SADS measures. The use of an instrument that looks more carefully at the symptoms of bipolar disorder, like the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (44), might have allowed more detailed data about the symptomatic presentation of these subjects to have been obtained.

During periods of mania, hypomania or mixed states, youths with BP-I may have moods that are irritable, elevated or both. It would have been useful to know how often each of these mood states was present during each of the youths' mood episodes. Many young people with BP-I may experience symptoms of both elevation and irritability. During the week prior to baseline in an ongoing clinical trial performed at this Center (41), 45 out of 66 subjects with bipolar disorder were found to have an elevated mood (defined as having a score greater than 1 on the 'Elevated Mood' item of the Young Mania Rating Scale (YMRS) (45). In addition, 42 out of these 66 young people were found to have an irritable mood during this period of time (receiving a score greater than 3 on the 'Irritability' item of the YMRS). Almost half of these subjects (30 out of 66) were found to have both an irritable and elevated mood at baseline during this clinical trial. It would also have been useful to know how symptomatic these patients were at the time of assessment. However, patients who present to this Center are generally quite symptomatic (41).

It should also be noted that this present study used multiple bivariate comparisons and a two-tailed alpha of 0.05 without Bonferroni adjustment. This strategy was employed due to concerns about having adequate statistical power to detect differences between children and teenagers. Using a Bonferroni-adjusted critical value of $p < 0.002$ to maintain an overall alpha < 0.05 for roughly 25 comparisons would have reduced the statistical power to an unacceptably low value of 0.30 for medium-sized effects (46, 47). Therefore, the analytic strategy was selected in order to maintain tolerable statistical power so that real differences between child and adolescent presentations of BP-I might be detected. Consideration of the actual values in the tables shows remarkable similarity between the child and adolescent cases of BP-I on almost all measured characteristics, an observation borne out by the statistical analyses.

It is interesting to note that only about one-half of this cohort had experienced a major depressive episode. However, the fact that depression is a less common mood state during the pre-adult years for patients with bipolar disorder is an observation that was made by Kraepelin (48). These subjects also had a relatively low rate of substance abuse disorders. This may be a reflection of the early-onset status of this group. In addition, a larger amount of these subjects' fathers had a bipolar spectrum disorder (42.9%) compared to the percentage of these patients' mothers who had a bipolar spectrum disorder (27.5%). Whether this reflects a genetic influence that contributed to the male preponderance of this sample remains to be seen.

Although concerns that distinction between ADHD and bipolar disorder may be difficult to make (5), these results are similar to those reported elsewhere. For example, Sachs et al. (49) noted that 62% of adults with early-onset bipolar disorder met diagnostic symptom criteria for ADHD. These results are similar to those of Geller et al. (50) who also found high rates of ADHD and other disruptive behavior disorders in early-onset cohort of juveniles with bipolar spectrum disorders (about half of whom had BP-1).

The results of this study suggest the possibility that juvenile BP-I might be a valid diagnosis and that the presentation of juvenile BP-I is on a continuum with the rapid cycling adult manifestations of this condition. When compared to adults, subjects in this cohort had high rates of rapid cycling and low rates of inter-episode recovery. The information provided from this study is clinically quite relevant as it might be used to inform clinicians on how to approach the evaluation of a young person for whom the diagnosis of a bipolar disorder might be suspected. These data suggest that meticulous assessments for the presence of different mood states, coupled with a careful family history and a thorough longitudinal consideration of symptomatology, could facilitate the accurate diagnosis of bipolar disorders in young people.

If the distinct manifestations of bipolar disorder in early age at onset patients remain consistent over time, then it would be important to identify the ages at onset for which 'mature' expressions of bipolar illness are more likely to be expressed. Similarly, it is also possible that these youths with BP-I will eventually have the manifestations of their illness change or 'mature' to more 'classical' adult expressions of this condition. Future longitudinal research should consider both of these possibilities as well as the underpinnings that lead to the developmentally mediated presentations of this illness. Further investigation should also be undertaken in order to either confirm or refute these findings.

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