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Original Article

Early symptoms of mania and the role of parental risk

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Objectives: The objectives of this study were to: (i) describe the phenomenology of youths diagnosed with subsyndromal bipolar disorders; (ii) describe the phenomenology of youngsters who are the children of bipolar parents, who are also experiencing subsyndromal symptoms of bipolar disorder (patients with 'cyclotaxia'); and (iii) explore which symptoms may be most useful in identifying youths with cyclotaxia.

Methods: Four hundred outpatients between the ages of 5 and 17 years received a diagnostic assessment and psychometric questionnaires pertaining to mood symptomatology and psychosocial functioning. Parental diagnostic information was also obtained. Children and adolescents were assigned to one of three diagnostic groups: a 'syndromal bipolar disorder (BP)' group (n = 118), a 'sub-syndromal bipolar (SUB-BP)' group (n = 75), or a 'non-bipolar (NON-BP)' group (n = 207). In addition, based on parental diagnoses, youths were assigned to either a high genetic risk group (n = 167) or a low genetic risk group (n = 233).

Results: Youths with subsyndromal bipolar disorders were found to have intermediate degrees of manic symptoms than youths with bipolar disorder and youths without a bipolar diagnosis. Offspring of parents having a bipolar disorder were more likely to show symptoms of hypomania and mania than youths without a bipolar parent. Youths at genetic risk for developing a bipolar disorder were not found to be at higher risk for having a diagnosis of attention-deficit hyperactivity disorder or a disruptive behavior disorder. Finally, results suggest that elevated mood with irritability and rapid mood fluctuations are the key distinguishing characteristics of 'cyclotaxia'.

Conclusions: There exists a group of youngsters who are the offspring of a parent/parents with a bipolar disorder who do not suffer from BP 1 or BP 2, yet have elevated mood symptoms and psychosocial dysfunction. As a result of these observations, treatment studies are needed for youths with 'cyclotaxia'.

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Bipolar disorder is a highly heritable condition (1, 2). It has been observed that offspring of parents with a bipolar disorder may have more emotional and behavior problems than youths without parents with a bipolar disorder (3). For this reason, clinicians and parents may wonder when a child of a parent with bipolar disorder is experiencing affective symptomatology, whether or not the child in question is showing early manifestations of a burgeoning mood disorder.

As many as 65% of adults with bipolar disorder have reported experiencing their first symptoms of this illness prior to adulthood (4). Furthermore, subsyndromal manifestations of bipolar disorder may antecede the full expression of this illness (5, 6). Although these patients with subsyndromal illness may not meet full diagnostic criteria for BP 1 or BP 2, subsyndromal symptoms may be debilitating to the patient and disruptive to the family environment (7, 8).

Young patients, who are early in the course of a mood disorder and are expressing subsyndromal symptoms may be potentially more amenable to treatment interventions (9). For this reason, an accurate description of the earliest manifestations of bipolar disorder may eventually allow for treatments to be developed that are aimed at early intervention and preventing the full expression of the illness (10).

The term 'schizotaxia' has been used to describe patients that are at genetic risk for developing schizophrenia and that are also demonstrating early symptoms of this illness (11). As there may be clinical benefit from early intervention for patients at risk of developing schizophrenia (12, 13), working diagnostic criteria for schizotaxia have been described (14). Akin to Meehl's conceptualization of schizotaxia as the prodromal variant of schizophrenia (11), subjects who are the offspring of a bipolar parent/parents and are experiencing subsyndromal symptoms of bipolar disorder have been referred to as showing characteristics of 'cyclotaxia' (15). Because of the growing prevalence rates reported in juvenile mania (16) as well as the vigorous research interest in identifying distinct phenotypes of bipolar spectrum disorders (BPSD) in young people (17, 18), the description of subsyndromal bipolarity also has substantial scientific importance. This avenue of research is similar to the work that has been done to validate bipolar 'spectrum' diagnostic constructs in adults, such as cyclothymia (19), bipolar II, and 'subthreshold' presentations (20).

For these reasons, a study was undertaken in order to describe the phenomenology of subsyndromal bipolar disorder in youths. It was hypothesized that youths suffering from a subsyndromal bipolar disorder [cyclothymia and BP-not otherwise specified (BP-NOS)] would show less mood symptomatology than youths diagnosed with the prototypic bipolar disorders. In addition, it was expected that patients with subsyndromal symptoms of bipolar disorder would experience more severe mood symptomatology than youths with other, non-bipolar psychiatric diagnoses. A second hypothesis was that children with a parental history of bipolar disorder would themselves show more mood symptoms than youths where neither biologic parent had a history of bipolar disorder. A third purpose of this study was to explore which symptoms could most accurately identify young people with 'cyclotaxia'. It was also hypothesized that mood symptoms might distinguish those children and adolescents with cyclotaxia from other youths.

Subjects and methods

Subjects

Families were recruited from a child and adult psychiatric research center and an adult mood disorders clinic at a mid-western academic medical center. Subjects were outpatients between the ages of 5 and 17 years. The participants for this study were recruited as part of the screening procedures for various treatment studies being performed at this center. A major focus of the research performed at this center is to provide treatment for children and adolescents with bipolar disorders.

Youths with no clinical evidence of a pervasive developmental order or mental retardation were eligible to be included in this present study. More information about the ascertainment of these subjects has been presented elsewhere (7). In addition, in order for a subject to be eligible for this study, subjects must also have had either: (i) both biologic parents complete a psychiatric assessment; or (ii) one parent demonstrating evidence of suffering from a bipolar disorder.

All procedures of this study were approved by the University Hospitals of Cleveland Institutional Review Board for Human Investigation. Written informed consent and assent of parents/guardians and subjects was obtained prior to participation in this study.

Subject diagnosis and symptomatology assessment

Eligible subjects and their parents/guardians were both interviewed by a highly trained rater over the course of two interviews. During the first interview, all children received a diagnostic assessment using the Schedule for Affective Disorders and Schizophrenia (SADS-LB) for School-Age Children-Epidemiological version (K-SADS-E) (21) or the -Present and Lifetime version (K-SADS-PL) (22). This semi-structured interview was performed by highly trained research assistants (12 Bachelor's level assistants, five Master's level assistants, and one Doctoral level interviewer). The training procedures, inter-rater reliability, and K-SADS

interview procedures used in this study have been described in more detail in a prior publication (7).

Following the administration of the K-SADS, the interviewer completed the Children's Depression Rating Scale-Revised (CDRS-R) (23) and the Young Mania Rating Scale (YMRS), and the Global Assessment of Functioning (GAF) (24). The primary caregiver also completed the Parent-completed General Behavior Inventory (25, 26) and the Child Behavior Checklist (CBCL) (27) as part of the initial screening assessment. It should be noted that the interviewer who performed the K-SADS interview did not have access to the results of the Parent General Behavior Inventory (P-GBI) during the diagnostic process. All diagnoses were reviewed by a board-certified child/adolescent psychiatrist. A physician and a psychometrician subsequently evaluated the patient (68.8% of the subjects, n = 275) if: (i) there was diagnostic uncertainty on the psychometrician's part, or (ii) a patient appeared to be eligible for participation in a treatment study being performed at this research center. The physician and interviewer would review the information collected in their separate interviews and come to a consensus diagnosis. In the rare cases where there was a disagreement between the structured interview and clinical assessment and a consensus diagnosis could not be reached, the data were not included in the analyses.

Unmodified DSM-IV criteria were used to assign diagnoses. It should be noted that only children and adolescents who experienced spontaneous, dysfunctional mood episodes that did not meet full criteria for any other mood disorder were given the diagnosis of BP-NOS.

Parental diagnosis

After the initial child/adolescent diagnostic assessment interview, the parents were assessed for the presence of psychiatric diagnoses. When parents could be interviewed directly, lifetime diagnoses were based upon the SADS-LB (28). If a parent could not be interviewed directly, either the Family History Research Diagnostic Criteria (FH-RDC) (29) interview was administered to the parent or a psychiatrist at University Hospitals of Cleveland had clinically assessed the parent in question.

Assessments

The Young Mania Rating Scale (30). The YMRS is a 11-item, clinician-administered instrument that assesses manic symptomatology along different levels of severity. Item scores range from 0 to 4 or from 0 to 8, with higher scores representing greater severity and impairment. Total scores may range from 0 to a maximum score of 56.

Children's Depression Rating Scale-Revised (23). The CDRS-R is a clinician-completed rating scale that is designed to measure depressive symptomatology. It consists of 17 items which are scored on a 5- or 7-point scale. Total scores on the CDRS-R can range from 17 to 113, with higher scores indicating greater severity of depression.

Parent General Behavior Inventory (25). The P-GBI is a 73-item, parent-completed measure that can probe for depressive and manic (or hypomanic) symptoms in child populations. The P-GBI items can be scored on a Likert scale, ranging from 0 (never or hardly ever) to 3 (very often or almost constantly), with higher scores indicating greater severity of psychopathology (26). The P-GBI produces depressive and hypomanic/biphasic subscores.

Child Behavior Checklist (27). This parent-completed measure is one of the most widely used instruments in both research and clinical practice with children. Item scores range from 0 (not true of the child) to 2 (very true or often true of the child). The broad groupings of syndromes that encompass an Internalizing subscore (composed of the anxious/depressed, withdrawn/depressed, and somatic complaints scales) and Externalizing subscore (composed of rule-breaking behavior and aggressive behavior scales) will be reported as *t*-scores in this study.

Global Assessment of Functioning (24). The GAF score ranges from 1 to 100, and reflects a patient's current psychological, social, and occupational functioning. Higher scores on the GAF-C reflect better psychosocial functioning.

Statistical analyses

For inclusion in the present study, 95% of the original item-level data from the YMRS, CDRS-R, and P-GBI needed to be complete and parent diagnostic information needed to be available.

Chi-square analyses and one-way analysis of variance (ANOVA) tests were used to determine whether there were differences in gender and age distribution between child diagnostic groups and groups defined by parental diagnosis. Likelihood ratios (also known as relative risks, or risk ratios) (31) were used to determine the change in

posterior odds associated with parental risk and a diagnosis of a BPSD (BP 1, BP 2, cyclothymia, and BP-NOS), attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (OpDD), and conduct disorder (CD). For purposes of this study, posterior odds are defined as the odds of having a diagnosis based on the combination of factors observed for that particular case. Furthermore, posterior odds are estimated using Bayes theorem, and are widely used in 'evidence-based medicine' approaches to assessment (31, 32).

T-tests were used to examine differences in the YMRS, CDRS-R, GAF, CBCL, and P-GBI between youths at genetic risk for developing bipolar disorder compared with youths not at genetic risk. In addition, one-way ANOVAs and Games-Howell *post hoc* tests examined differences between children and adolescents who had a parent with a bipolar disorder and assigned them to a 'syndromal bipolar disorder (BP)' group, a 'subsyndromal bipolar (SUB-BP)' group, and a 'non-bipolar (NON-BP)' group. The Games-Howell *post hoc* tests were used in this study due to this test being one of the few *post hoc* procedures that shows robust performance in situations where group sizes are unequal and also when within-group variances are unequal (i.e., when the assumption of homogeneity of variance is violated). The present analyses involve both unequal group sizes and variances, so Games-Howell becomes the preferred *post hoc* procedure according to Kirk (33).

Finally, two exploratory forward stepwise logistic regression analyses were performed to predict key symptoms on the (i) P-GBI items, and (ii) YMRS and CDRS-R measures in an attempt to determine those symptoms that discriminate those patients at genetic risk are showing symptoms of a subsyndromal bipolar disorder compared with patients without a bipolar disorder. For this study, the goal of the logistic regressions was not formal hypothesis testing. These analyses were performed to complement bivariate analyses by identifying symptoms that provide unique or incremental information differentiating between the groups. Although stepwise entry is problematic in a 'hypothesis testing' framework, because these results are intended to be exploratory, it is appropriate as a descriptive method of summarizing variables that discriminate groups (34).The alpha level for statistical significance was set at $p \leq 0.05$. Because of the exploratory nature of this study, the alpha level for statistical significance was not adjusted for the multiple comparisons performed in this study.

Results

Subjects

A total of 400 patients with a mean age of 11.3 (3.2) years were enrolled in this study. Of these, 245 were male and 155 were female. The majority of the participants were Caucasian (n = 334, 83.5%), and the remainder of the subjects were African-American (n = 39, 9.8%), Biracial (n = 15, 3.8%), Hispanic (n = 9, 2.3%), native American/Alaskan native (n = 2, 0.5%), and one respondent did not indicate his/her race (n = 1, 0.3%). Multiple children within a family were eligible to enroll in this study. In this study, 31 sets of two siblings, three sets of three siblings, and one set of four siblings were included.

Subject diagnoses

Of the 400 subjects completing a K-SADS interview, 275 (68.8%) also completed a direct clinical assessment by a child and adolescent psychiatrist, confirming the K-SADS interview results. Children and adolescents were placed into three diagnostic comparison groups. These diagnostic groups included a BP group, a SUB-BP group, and a NON-BP group (see Fig. 1). The BP group (n = 118, 29.5%) was composed of 114 (96.6%) patients with a diagnosis of BP 1 and four (3.4%) patients with a diagnosis of BP 2. The SUB-BP group (n = 75, 18.8%) included 44 (58.7%) patients diagnosed with BP-NOS and 31 (41.3%) with cyclothymia. The NON-BP group contained 207 (51.7%) youths with other psychiatric diagnoses (n = 165, 79.7%) or those subjects found to have no diagnosis (n = 42, 20.3%). Table 1 contains a listing of the subjects contained in each group and the occurrence of comorbid ADHD which was the most common comorbidity seen in these subjects.

A chi-square analysis indicated no differences in the distribution of gender across the three diagnostic groups. The three groups did show significant differences in mean age ($F_{2,397} = 5.63$, $p < 0.005$). Using the Games-Howell test to determine reliable *post hoc* group differences, the

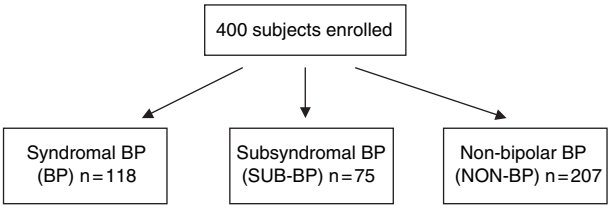

Fig. 1. Patient diagnostic groups.

Table 1. Demographic information for 400 youth assigned to 'syndromal bipolar (BP),' 'sub-syndromal bipolar (SUB-BP),' and 'non-bipolar (NON-BP)' diagnostic groups

	Syndromal (BP)	Subsyndromal (SUB-BP)	Non-bipolar (NON-BP)	Total subjects
Number of youths	118 (29.5)	75 (18.8)	207 (51.7)	400
Mean age (SD)	10.6 (3.2)	10.9 (3.1)	11.8 (3.2)	11.3 (3.2)
Number of males	78 (66.1)	49 (65.3)	118 (57.0)	245 (61.2)
Primary diagnoses				
Mood disorders				
BP 1	114 (96.6)	0	0	114 (28.5)
Comorbid ADHD/DBDs	82 (71.9)/49 (43.0)	0	0	82 (71.9)/49 (43.0)
BP 2	4 (3.4)	0	0	4 (1.0)
Comorbid ADHD/DBDs	2 (50.0)/1 (25.0)	0	0	2 (50.0)/1 (25.0)
Cyclothymia	0	31 (41.3)	0	31 (7.8)
Comorbid ADHD/DBDs	0	19 (61.3)/12 (38.7)	0	19 (61.3)/12 (38.7)
BP-NOS	0	44 (58.7)	0	44 (11.0)
Comorbid ADHD/DBDs	0	28 (63.6)/12 (27.3)	0	28 (63.6)/12 (27.3)
Unipolar mood disorder	0	0	86 (41.5)	86 (21.5)
Other disorders (without a comorbid affective illness)				
ADHD	0	0	58 (28.0)	58 (14.5)
Disruptive behavior disorders	0	0	6 (2.9)	6 (1.5)
Substance abuse	0	0	2 (1.0)	2 (0.5)
Psychotic spectrum disorders	0	0	4 (1.9)	4 (1.0)
Anxiety disorders	0	0	6 (2.9)	6 (1.5)
Adjustment disorder	0	0	2 (1.0)	2 (0.5)
Enuresis	0	0	1 (0.5)	1 (0.3)
No reported axis I disorders	0	0	42 (20.3)	42 (10.5)

Data are presented as n (%) unless otherwise specified. BP 1 = bipolar disorder 1; BP 2 = bipolar disorder 2; BP-NOS = BP-not otherwise specified; ADHD = Attention-Deficit Hyperactivity Disorder; DBDs = Oppositional Defiant Disorder and Conduct Disorder.

NON-BP group's mean age (11.8, SD = 3.2) was significantly higher than the BP group's mean age (10.6, SD = 3.2; $p < 0.005$).

Group assignment by parental diagnosis

Of the 400 subjects, in 356 (89.0%) cases, both parents were assessed for psychiatric diagnoses. The remaining 44 subjects had one parent who met diagnostic criteria for a bipolar disorder based on a clinical interview. Four hundred seventy four (59.3%) parents were assessed with the SADS-LB and 255 (31.9%) parents were assessed by the FH-RDC, 27 (3.4%) were assessed by a psychiatrist within the Mood Disorders Program at University Hospitals of Cleveland, and 44 (5.5%) parents' diagnoses were not known. Parent diagnoses are shown in Table 2.

Table 2. Parent diagnoses for 400 youth at genetic high-risk or not at-risk for developing BPSD

	Mother (n = 397)	Father (n = 359)	Overall (n = 756)
Primary diagnoses (%)			
Mood disorders			
BP 1	69 (17.4)	58 (16.2)	127 (16.8)
BP 2	29 (7.3)	9 (2.5)	38 (5.0)
Cyclothymia	3 (0.8)	8 (2.2)	11 (1.5)
BP-NOS	6 (1.5)	3 (0.8)	9 (1.2)
Unipolar mood disorder	106 (26.7)	27 (7.5)	133 (17.6)
Non-affective illnesses			
Substance abuse/dependence	6 (1.5)	61 (17.0)	67 (8.9)
Other disorders	21 (5.3)	16 (4.5)	37 (4.9)
No reported axis I disorders	157 (39.5)	177 (49.3)	334 (44.2)

BPSD = bipolar spectrum disorders; BP 1 = bipolar disorder 1; BP 2 = bipolar disorder 2; BP-NOS = BP-not otherwise specified.

Familial risk groups were assigned based on the results of the parents' diagnostic assessment. Within the current study, youths were defined as being 'high risk' (HR) if they had at least one parent with BP 1, BP 2, or another BPSD. All other patients were included in the 'low risk' (LR) group (see Fig. 2). One hundred sixty seven (41.8%) participants had a least one parent with a bipolar disorder (HR) and 233 (58.2%) did not have a parent with a bipolar disorder (LR). Chi-square and *t*-test analyses indicated there were no differences in gender and age distribution between the HR and LR groups ($p > 0.05$).

Child diagnoses and parental bipolarity

The most frequent primary child diagnoses in the HR group included syndromal bipolar disorders (BP 1 and BP 2), subsyndromal bipolar disorders

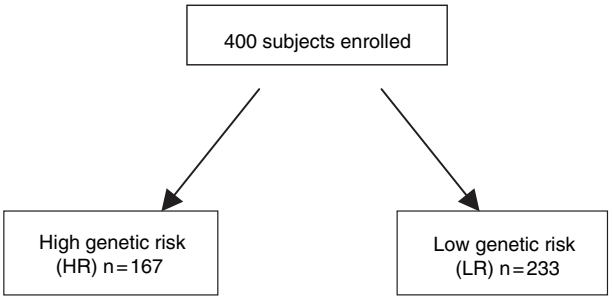

Fig. 2. Comparison groups based on parental diagnosis.

(cyclothymia and BP-NOS), and no diagnosis. In the LR group, the most frequent diagnoses were depressive disorders [major depression disorder (MDD), dysthymic disorder, and depressive disorder NOS], syndromal bipolar disorders (BP 1 and BP 2), ADHD, and no diagnosis. A listing of child diagnoses across parental diagnostic groups can be found in Table 3.

Youths with a bipolar parent (HR) showed higher rates of mood disorder (odds ratio = 2.9, chi-square = 20.51, $p < 0.0005$), particularly bipolar disorders (bipolar 1, 2, cyclothymia, or bipolar NOS) (odds ratio = 6.5, chi-square = 74.09 with 1 df, $p < 0.0005$) than those in the LR group. Of the 193 youths meeting criteria for any bipolar disorder, 123 had at least one parent with a lifetime diagnosis of a bipolar disorder. The subjects in the HR group were not at higher risk of having a primary or comorbid diagnosis of ADHD (odds ratio = 1.1, chi-square = 0.43 with 1 df, $p > 0.05$), OpDD (odds ratio = 1.5, chi-square = 3.08 with 1 df, $p > 0.05$), or CD (odds ratio = 1.0, chi-square = 0.01 with 1 df, $p > 0.05$).

Genetic risk and psychopathology

In order to examine the impact of parental diagnosis on the subject's psychiatric and psychosocial symptoms, the YMRS, CDRS-R, P-GBI, CBCL, and GAF scores in the HR group were compared with the LR group. Mean scores on the YMRS, CDRS-R, P-GBI, CBCL, and GAF are listed in Table 4. Correlations between the YMRS total score, CDRS-R total score, P-GBI Depression subscale score, and P-GBI Hypomanic/Biphasic subscale score are shown in Table 5.

Young Mania Rating Scale and genetic risk

Total YMRS mean scores significantly differed between the HR group (15.7, SD = 11.1) and the LR group (8.2, SD = 12.3) ($t = 6.29$, df = 398, $p < 0.0005$). Moreover, the HR group exhibited higher scores compared with the LR group on all

Table 3. Demographic information for 400 youth at high genetic risk (HR) or low genetic risk (LR) for developing BPSD

	HR	LR	Total subjects
Number of youths	167 (41.8)	233 (58.2)	400
Mean age (SD)	11.0 (3.4)	11.5 (3.1)	11.3 (3.2)
Number of males	99 (59.3)	146 (62.7)	245 (61.2)
Primary diagnoses			
Mood disorders			
BP 1	62 (37.1)	52 (22.3)	114 (28.5)
Comorbid ADHD/DBDs	43 (69.4)/28 (45.2)	39 (75.0)/21 (40.4)	82 (71.9)/49 (43.0)
BP 2	3 (1.8)	1 (0.4)	4 (1.0)
Comorbid ADHD/DBDs	2 (66.7)/1 (33.3)	0	2 (50.0)/1 (25.0)
Cyclothymia	25 (15.0)	6 (2.6)	31 (7.8)
Comorbid ADHD/DBDs	16 (64.0)/9 (36.0)	3 (50.0)/3 (50.0)	19 (61.3)/12 (38.7)
BP-NOS	33 (19.8)	11 (4.7)	44 (11.0)
Comorbid ADHD/DBDs	21 (63.6)/11 (33.3)	7 (63.6)/1 (9.1)	28 (63.6)/14 (31.8)
Unipolar mood disorder	14 (8.4)	72 (30.9)	86 (21.5)
Other disorders			
ADHD	7 (4.2)	51 (21.9)	58 (14.5)
Disruptive behavior disorders	0	6 (2.6)	6 (1.5)
Substance abuse	0	2 (0.9)	2 (0.5)
Psychotic spectrum disorders	1 (0.6)	3 (1.3)	4 (1.0)
Anxiety disorders	2 (1.2)	4 (1.7)	6 (1.5)
Adjustment disorder	1 (0.6)	1 (0.4)	2 (0.5)
Enuresis	0	1 (0.4)	1 (0.3)
No reported axis I disorders	19 (11.4)	23 (9.9)	42 (10.5)

Data are presented as n (%) unless otherwise specified. BPSD = bipolar spectrum disorders; BP 1 = bipolar disorder 1; BP 2 = bipolar disorder 2; BP-NOS = BP-not otherwise specified; ADHD = Attention-Deficit Hyperactivity Disorder; DBDs = Oppositional Defiant Disorder and Conduct Disorder.

Table 4. Mean (SD) mood and behavior rating scores in the youths at high genetic risk (HR) and low genetic risk (LR) for bipolar disorder

	Risk group			
	HR (n = 167)	LR (n = 233)	Overall (n = 400)	Significance
YMRS	15.7 (11.1)	8.2 (12.3)	11.3 (12.4)	<0.0005
P-GBI Hypomanic/Biphasic	30.1 (18.0)	21.3 (16.3)	25.0 (17.5)	<0.0005
P-GBI Depression	39.3 (26.4)	34.1 (26.5)	36.3 (26.5)	>0.05
GAF	57.9 (12.5)	56.2 (15.8)	56.9 (14.6)	>0.05
CDRS-R	31.7 (14.1)	35.8 (18.7)	34.1 (17.1)	<0.05
CBCL subscale scores				
Externalizing	67.7 (13.4)	63.6 (12.8)	65.3 (13.2)	<0.01
Internalizing	65.3 (12.9)	64.0 (12.2)	64.5 (12.5)	>0.05

YMRS = Young Mania Rating Scale; P-GBI = Parent General Behavior Inventory; GAF = Global Assessment of Functioning; CDRS-R = Children's Depression Rating Scale-Revised; CBCL = Child Behavior Checklist.
Mean scores between HR and LR groups compared using independent *t*-tests.

Table 5. Correlations between the Young Mania Rating Scale (YMRS) total score, Children's Depression Rating Scale (CDRS-R) total score, P-GBI Depression subscale score, and P-GBI Hypomanic/Biphasic subscale score

	CDRS	YMRS	P-GBI Depression subscale	P-GBI Hypomanic/Biphasic subscale
CDRS	1.00	−0.05	0.56***	0.15**
YMRS	−0.05	1.00	0.26***	0.60***
P-GBI Depression subscale	0.56***	0.26***	1.00	0.70***

P-GBI = Parent General Behavior Inventory. **p < 0.005, ***p < 0.0005 (two-tailed).

of the items of the YMRS (all p-values < 0.05) indicating that, overall, youths at genetic risk experience more severe hypomanic and manic symptoms than others.

Children's Depression Rating Scale-Revised and parental diagnosis

A significant difference in the CDRS-R total score between the HR group (31.7, SD = 14.1) and the LR group (35.8, SD = 18.7) ($t = 2.39$, df = 398, $p < 0.05$) was found. Overall, the LR group reported higher scores compared with the HR group on several CDRS-R items. More specifically, there was a significant difference in the schoolwork ($t = 3.50$, df = 398, $p < 0.005$), difficulty with sleep (middle) ($t = 2.68$, df = 264, $p < 0.01$), excessive fatigue (2.53, df = 398, $p < 0.05$), weeping ($t = 3.00$, df = 398, $p < 0.005$), depressed affect ($t = 2.94$, df = 398, $p < 0.005$), tempo of speech ($t = 2.35$, df = 398, $p < 0.05$), and hypoactivity ($t = 2.45$, df = 398, $p < 0.05$) items between the HR and LR groups.

Parent General Behavior Inventory and parental diagnosis

The HR group reported higher P-GBI Hypomanic/Biphasic subscale scores, reflecting more severe hypomania/mania symptomatology, compared with the LR group ($t = 5.07$, df = 397, $p < 0.005$). However, P-GBI depression subscale scores did not significantly differ between the HR and LR groups ($t = 1.94$, df = 397, $p > 0.05$).

Child Behavior Checklist and parental diagnosis

The mean Externalizing *t*-score of the CBCL in the HR group (67.7, SD = 13.4) significantly differed from the LR group (63.6, SD = 12.8) ($t = 2.86$, df = 339, $p < 0.01$). However, the HR group did not significantly differ from the LR group on the CBCL Internalizing *t*-score ($t = 0.91$, df = 339, $p > 0.05$).

Global Assessment of Functioning and parental diagnosis

For all subjects the mean GAF score was 56.9 (SD = 14.6). The GAF score did not significantly differ between the HR group (57.9, SD = 12.5) and the LR group (56.2, SD = 15.8) ($t = 0.96$, df = 295, $p > 0.05$).

Youths at genetic risk and mood symptomatology

To explore symptomatic differences between diagnostic groups within the HR group, analyses were performed specifically in this subject sub-group. As before, HR subjects were separated into BP,

Table 6. Mean scores and analysis of variance (ANOVA) results in youths at high genetic risk for developing a bipolar disorder

	Child diagnostic group			ANOVA results		
	Syndromal (BP) (n = 65)	Subsyndromal (SUB-BP) (n = 58)	Non-bipolar (NON-BP) (n = 44)	*F*	df	Significance
YMRS	25.1 (6.3)	15.9 (6.8)	1.7 (4.8)	192.1	2,164	<0.0005
P-GBI Hypomanic/Biphasic	40.7 (14.7)	31.8 (13.6)	12.2 (13.2)	55.6	2,163	<0.0005
P-GBI Depression	51.2 (24.9)	38.5 (21.3)	22.7 (25.5)	18.6	2,163	<0.0005
GAF	52.4 (7.0)	56.6 (7.3)	70.4 (17.5)	25.8	2,110	<0.0005
CDRS-R	34.9 (15.1)	30.9 (10.9)	28.1 (15.6)	3.33	2,164	0.038
CBCL subscale scores						
Externalizing[a]	74.0 (7.9)	71.4 (7.5)	54.2 (15.6)	44.6	2,136	<0.0005
Internalizing[a]	68.4 (10.4)	67.5 (9.8)	58.1 (16.4)	9.3	2,136	<0.0005

Data are presented as mean (SD). YMRS = Young Mania Rating Scale; P-GBI = Parent General Behavior Inventory; GAF = Global Assessment of Functioning; CDRS-R = Children's Depression Rating Scale-Revised; CBCL = Child Behavior Checklist.
Total score unless otherwise noted. All three diagnostic groups' means differed significantly ($p < 0.05$) in *post hoc* Games-Howell analyses unless otherwise noted.
[a]Syndromal and subsyndromal diagnostic groups did not differ significantly in *post hoc* Games-Howell analyses.

SUB-BP, and NON-BP diagnostic groups. Of the 167 subjects in the HR group, 65 (38.9%) subjects belonged in the BP diagnostic group, 58 (34.7%) in the SUB-BP diagnostic group, and 44 (26.3%) in the NON-BP group.

One-way ANOVAs were performed to compare mood symptomatology and psychosocial functioning between the diagnostic groups. The one-way analyses indicated a significant difference between the three groups on the YMRS total score, P-GBI Hypomanic/Biphasic and Depression subscores, GAF score, and the Externalizing and Internalizing CBCL subscales (all p-values <0.05). There were also significant overall differences on the CDRS-R, ($F_{2,164} = 3.33$, $p = 0.038$); however, the differences were not large enough to achieve $p < 0.05$ on any of the *post hoc* comparisons.

In order to explore specific differences across diagnostic groups, Games-Howell *post hoc* tests were subsequently used. These *post hoc* tests indicated significant differences between all three diagnostic groups in the HR population on the YMRS, P-GBI Hypomanic/Biphasic and Depression subscores, and the GAF score (all p-values <0.05). Furthermore, *post hoc* tests indicated a significant difference between the BP group and the NON-BP group on the Externalizing and Internalizing subscales of the CBCL (all p-values <0.05). Mean scores and ANOVA results are shown in Table 6.

Predicting patient diagnosis in youths at high risk for developing a bipolar disorder

To determine the distinguishing features of youths at genetic risk for developing a bipolar disorder who may have a subsyndromal bipolar diagnosis (patients with 'cyclotaxia'), logistic regression was used to compare the BP group with the NON-BP group. Two exploratory forward stepwise logistic regression analyses ($p < 0.05$ as inclusion criteria) were employed in order to examine which variables among the parent report items (P-GBI) and the clinician-rated mood symptom (CDRS-R; YMRS) best predicted the appropriate diagnostic group assignment of those individuals in the HR group.

Predictors of a subsyndromal bipolar diagnosis using the Parent General Behavior Inventory

The first logistic regression analysis found that five items on the P-GBI (Table 7) best predicted assignment of youths to the subsyndromal diagnostic group. The model including these five predictors was highly significant ($\chi^2 = 77.32$, $df = 5$, $p < 0.0005$).

When examining the five P-GBI variables from the logistic regression in a univariate fashion, rapid changes in mood from happy to sad (Wald score = 33.91, $p < 0.005$) and irritability during elevated mood periods (Wald score = 27.54, $p < 0.005$) were the best predictors for HR youths to meet diagnostic criteria for a subsyndromal bipolar disorder. The 'brooding' and 'sleep disturbance' items did not discriminate between the groups by themselves, but were significant only after controlling for the other mood items listed above that were included in the multivariate model.

Predictors of a subsyndromal bipolar diagnosis using the Young Mania Rating Scale and Children's Depression Rating Scale-Revised

A second logistic regression analysis was utilized to determine which combination of the clinician-rated

Table 7. Items of the P-GBI, YMRS, and CDRS-R that significantly predict patient diagnosis in youths at high risk for developing a bipolar disorder

Measures	β	SE (β)
P-GBI logistic regression analysis (Hypo/Manic and Depression Scales)[a]		
Item 19[b]: 'Has your child's mood or energy shifted rapidly back and forth from happy to sad or high to low?'	5.04***	1.49
Item 20: 'Have there been periods lasting several days or more when your child spent much of his/her time brooding about unpleasant things that have happened?'	−3.72[c]**	1.29
Item 37: 'Has your child had times of several days or more when he/she woke up frequently or had trouble staying asleep during the middle of the night?'	−2.30[c]**	0.82
Item 42: 'Have there been times when your child had a strong urge to do something mischievous, destructive, risky, or shocking?'	−1.50*	0.81
Item 54[b]: 'Have there been periods when, although your child was feeling unusually happy and intensely energetic, almost everything got on his/her nerves and make him/her irritable or angry (other than related to the menstrual cycle)?'	3.69**	1.23
YMRS and CDRS-R logistic regression analysis[d]		
YMRS: Item 1 (elevated mood)	2.44***	0.55
YMRS: Item 9 (disruptive aggressive behavior)	1.19**	0.40
CDRS-R: Item 11 (depressed feelings)	−1.05[c]*	0.48
CDRS-R: Item 15 (depressed affect)	1.37[c]*	0.53

P-GBI = Parent General Behavior Inventory; YMRS = Young Mania Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised.
*$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$.
[a]Final model chi-square = 77.32, df = 5, $p < 0.0005$.
[b]Key items that discriminate youths with 'cyclotaxia' and all other diagnostic groups.
[c]These predictors did not significantly differentiate the groups by themselves, but they did contribute unique incremental information after controlling for the other variables in the model.
[d]Final model chi-square = 95.07, df = 4, $p < 0.0005$.

CDRS-R and the YMRS items best predicted individuals who were HR and showed symptoms of a subsyndromal mood disorder in this sample. Of the manic and depressive symptoms, the elevated mood and disruptive/aggressive behavior items from the YMRS and depressed feelings and depressed affect items of the CDRS-R best predicted which HR youth would suffer from a subsyndromal bipolar diagnosis. The model including these four predictors was highly significant ($\chi^2 = 95.07$, df = 4, $p < 0.0005$) (Table 7).

When the elevated mood and disruptive/aggressive behavior of the YMRS and depressed feelings and depressed affect items of the CDRS-R were examined independently of the model, it was found that the elevated mood (Wald score = 58.35, $p < 0.005$) and disruptive/aggressive behavior (Wald score = 36.94, $p < 0.005$) items of the YMRS were the best predictors of the HR children and adolescents to be included in the subsyndromal bipolar disorder group. Depressed symptoms did not discriminate between the groups by themselves, only contributing significant statistical information after controlling for the elated mood and disruptive aggressive symptoms.

It should be noted that controlling for age did not affect the results for manic symptoms, but made the differences in depressive symptoms no longer significant due to the positive correlation between age and depression.

Discussion

This study found distinct differences in mood symptom severity in children and adolescents who meet diagnostic symptom criteria for syndromal bipolar disorders (BP 1 and BP 2), subsyndromal bipolar disorders (BP-NOS and cyclothymia), and other psychiatric diagnoses. Although youths diagnosed with a subsyndromal bipolar disorder may not meet full symptom criteria for a syndromal bipolar disorder, the results of the study suggest that these youngsters are both debilitated and have substantial mood symptomatology. These impaired youths with subsyndromal symptoms suggest the need for effective early identification and intervention (10).

In addition, these results indicate that the offspring of parents having a bipolar disorder are significantly more likely to show symptoms of hypomania and mania than are youths without a bipolar parent. The increase in risk for mood disorders in general and bipolar spectrum illness in particular observed in this study aligns well with the results of a recent meta-analysis of familial risk in offspring with a bipolar parent (3). Although

high rates of comorbid ADHD and disruptive behavior disorders (DBD) with pediatric bipolarity have been reported elsewhere (7, 35), the risk of ADHD and DBDs did not differ significantly between the HR and LR groups. This finding suggests that the relative elevations in hypomanic symptomatology are attributable to mood disturbance and not hyperactivity/impulsivity that is associated with ADHD or a DBD.

The case for a patient population with 'cyclotaxia'

Based on these results, it appears that there is evidence for a prodromal expression of bipolar disorder, similar to Meehl's conceptualization of schizotaxia as a prodromal variant of schizophrenia (11). Based on clinical observation at this center, we had previously hypothesized that cyclotaxia, a prodromal manifestation of bipolar disorder in genetically at-risk youths, described a clinically relevant group of patients. The results of this study help identify a clinically salient population of youngsters at genetic HR with mood symptoms and psychosocial dysfunction.

Clinical applicability

It appears that elevated mood with irritability and rapid fluctuations in mood are key distinguishing symptoms of HR youths who are suffering from subsyndromal mood disorders. Although parents often seek treatment for their children due to other problematic symptoms, such as aggression and irritability, it appears that the symptom of abnormally elevated mood is the best predictor of a possible subsyndromal manifestation of a bipolar disorder. These results mirror a previous finding from this center in which abnormally elevated mood was found to be the best single symptom in delineating 'syndromal' bipolar disorders from other disorders (E. A. Youngstrom, unpublished data). In addition, clinicians who are attempting to determine whether a youth might be experiencing early symptoms of bipolar disorder might wish to enquire about the presence or absence of sleep disturbances, brooding, and impulsive risky/dangerous behaviors, particularly when occurring in the context of other changes in mood or energy.

Strengths and limitations

This study contained a large heterogeneous sample of participants who completed a rigorous diagnostic assessment. Limitations of this study include that the sample is clinical and not epidemiological in nature, and that familial risk was only assessed in parents. Familial risk assessments neither included siblings nor second-degree relatives. Thus there is a potential for bias, where families assigned to the LR group might actually have a history of bipolar disorder in other family members. This would act to lessen the differences between the groups, making it even less likely to find the significant results that are reported herein. Furthermore, not all parents were directly interviewed to establish a diagnosis. Therefore, if a parent was not available for a direct interview the diagnostic information was collected via an interview with the parent present. Another limitation was that the various mood and behavioral ratings were correlated with each other, introducing some redundancy in the findings when the scales were analyzed separately. It should also be noted that the procedures employed in the logistic regression analyses were exploratory. Furthermore, as the recruitment of patients was from a research center which treats bipolar disorder, the results of this study may not be as generalizable as epidemiological studies. For this reason, the 'cyclotaxia' construct needs to be further examined in community-based samples in order to further delineate the characteristics of this patient group.

Future directions for research

Future studies need to clarify the diagnostic boundaries of 'cyclotaxia,' identifying key symptoms and establishing stringent evidence-based diagnostic symptom criteria. The patient group described as having symptoms of 'cyclotaxia' will require further research in order to confirm or reject its clinical validity. These results contribute to the current discussion about the 'broad phenotype' of juvenile bipolar disorder (17, 18) by showing that a biologically at-risk group of youths differ from a psychiatric comparison group. The at-risk group differed from the psychiatric comparison group in terms of hypomanic symptoms, independent of other disruptive behavior diagnoses. In addition, future studies will need to be conducted to determine the longitudinal course of these patients in order to determine whether 'cyclotaxia' is truly prodromal to full bipolar disorder.

Conclusion

In conclusion, it appears that there is a group of youths who are at genetic risk for developing bipolar disorder that have substantial mood symptomatology and psychosocial dysfunction. Furthermore, family history of bipolar disorder is

associated with an increased risk of subsyndromal bipolar disorders and not just fully syndromal bipolar disorder.

As a result, these patients with 'cyclotaxia' are in need for accurate and effective intervention. The two key features of 'cyclotaxia' appear to be irritability during periods of elation and rapid changes in mood.

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