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Are obstetrical, perinatal, and infantile difficulties associated with pediatric bipolar disorder?

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Abstract

Objectives—Despite increasing acknowledgement of Bipolar Disorder (BD) in childhood, there is a paucity of literature that has investigated obstetrical, perinatal, and infantile difficulties and their potential link with BD. To this end, we examined difficulties during delivery, immediate post-birth, and infancy and the association with BD in childhood.

Methods—From two similar-designed ongoing longitudinal, case-control family studies of pediatric BD (N=327 families), we analyzed 338 children and adolescents (mean age: 12.00 ± 3.37 years). We stratified them into three groups: healthy controls (N=98), BD probands (N=120), and their non-affected siblings (N=120). All families were comprehensively assessed with a structured psychiatric diagnostic interview for psychopathology and substance use. Mothers were directly questioned regarding the pregnancy, delivery, and infancy difficulties that occurred with each child using a module from the Diagnostic Interview for Children and Adolescents-Parent Version (DICA-P).

Results—Mothers of BD subjects were more likely to report difficulties during infancy than mothers of controls (Odds Ratio (95% CI) = 6.6 (3.0, 14.6)). Specifically, children with BD were more likely to have been reported as a stiffened infant (7.2 (1.1, 47.1)) and more likely to have experienced “other” infantile difficulties (including acting colicky; 4.9 (1.3, 18.8)) compared to controls. We found no significant differences between groups in regards to obstetrical or perinatal difficulties (all p values > 0.05).

Conclusions—While our results add to previous literature on obstetrical and perinatal difficulties and BD, they also highlight characteristics in infancy that may be prognostic indicators for pediatric BD.

Keywords

bipolar disorder; perinatal; obstetrical complications

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Introduction

Pediatric Bipolar Disorder (BD) has recently been reported to occur in 2.9% of the general pediatric population(1) and is associated with substantial morbidity, hospitalizations, and problems in the home environment.(2–7) While previous research shows strong familial links and highlights probable genetic causes associated with the development of pediatric BD,(8–11) concordance rates of less than 100% in studies of monozygotic twins prove that environmental factors such as complications pre- and post-birth may also play a role in the development of BD.(12) Specifically, among six twin studies of “manic-depressive disorder,” only 60% of the variance in bipolar disorder was related to genetic factors.(13) Obstetrical and perinatal stressors are among the environmental sources that may affect psychiatric illness.

Obstetrical complications have been linked with other psychiatric disorders such as adult schizophrenia(14, 15); however, less is known about their role in other disorders including BD. It is posited that obstetrical complications may impair prenatal or perinatal brain development and may be associated with brain abnormalities reported in neuro-imagining studies of BD individuals.(16) For example, a smaller amygdala has been reported in pediatric BD(17, 18) and schizophrenic patients, and has been associated with obstetrical complications in schizophrenia.(19) Likewise, total cerebrum volume was reported to be significantly reduced in both schizophrenic and BD patients compared to controls.(20) It was posited that this reduction may have resulted from a first trimester impairment or a perinatal insult in the third trimester.(21)

While previous research has examined the role of obstetrical complications and BD, most of this research is predominantly among adults, small samples, and with mixed results.(15, 16, 22, 23) For example, Kinney et al. found that adult BD probands (N=30) were more likely to have higher scores for obstetrical complications than their non-mood disordered adult siblings (N=25). (23) In contrast, Scott et al.’s meta-analysis found a null-pooled odds ratio for the exposure to obstetrical complications and subsequent BD when comparing BD cases and controls across 8 studies, a majority of which were small, adult samples.(16) These inconsistent results could be due to differences in the comparison groups (BD probands vs. siblings or BD probands vs. non-mood disordered controls) and the measurement of obstetrical complications.

In addition to studying obstetrical complications and perinatal insults that may lead to BD, it is also important to examine early childhood characteristics. Early childhood characteristics have been reported to be identifiable manifestations of later psychological dysfunction or as precursors that increase the risk of developing certain psychological disorders.(24, 25) In a sample of adolescents, West et al. found that parents of children with BD were more likely to retrospectively report difficult “temperaments” in both infancy and toddlerhood, compared to controls or adolescents with Attention Deficit/Hyperactivity Disorder (ADHD). (26) Specifically, parents of children with BD were more likely to report that their children experienced more difficulty sleeping, difficulty being consoled, acting colicky, and excessive crying among others.(26) Identifying childhood characteristics that may show early signs of later psychopathology could allow for the identification of associated behaviors and early interventions.(25)

We looked to examine whether obstetrical and perinatal difficulties were related to pediatric BD by comparing probands and non-mood disordered controls as well as by comparing probands and their age-matched, non-affected siblings. In using non-affected siblings, we hoped to eliminate much of the confounding that can occur in comparing children of different mothers, including the likelihood of a mother to experience obstetrical

complications. In addition to examining the role of obstetrical complications, we also investigated whether characteristics after birth were linked to the later development of pediatric BD. By examining issues in infant behavior after birth, we aimed to find associated features of BD that may be prognostic indicators. The role of obstetrical complications in the development of pediatric BD and the knowledge of prognostic indicators are of great importance for the etiology, prevention, and treatment of BD. Based on the limited literature, we hypothesized that there would be more obstetrical and perinatal difficulties in youth with BD compared to their non-affected siblings as well as compared to controls. We also hypothesized that youth with BD would be more likely to be described as having difficulties during infancy compared to their non-affected siblings and controls.

Materials and Methods

Subjects

Subjects were from two similar-designed ongoing longitudinal, case-control family studies (Juvenile Bipolar Disorder and Substance Use Disorder (BD/SUD); Childhood Mania) of BD children and adolescents. The detailed methods of both of these studies have been reported previously.(27, 28) For the Mania study, we recruited youth with BD. For the BD/SUD study, we recruited youth and adolescents with BD as well as non-mood disordered control subjects. Subjects from both studies were ascertained from the same catchment area through the use of newspaper advertisements, internet postings, clinical referrals (BD study subjects only), and internal posting in the extended hospital system.

Both studies employed a two-stage ascertainment process to select BD subjects, if they were not clinically referred into the study. The first stage assessed the diagnosis of BD by screening all children using a telephone questionnaire, which queried about symptoms of BD and study exclusion criteria, conducted with the primary caregiver. The second stage confirmed the diagnosis of BD using a structured psychiatric interview, as described below. Only subjects who received a positive diagnosis at both stages were included in the study sample. Non-mood disordered controls were also screened in two stages in the BD/SUD study. First, control primary caregivers responded to the telephone questionnaire, then eligible controls meeting study entry criteria were recruited and received a diagnostic assessment through a structured interview. Only subjects classified as not having any mood disorder at both stages were included in the control group. We excluded controls with any mood disorder because of concerns about potential “manic switching” from dysthymia or unipolar depression to BD.(5)

All families with a child or adolescent (designated as the proband) who was between 4 and 18 years of age for the Mania study and who was between 10 and 18 years of age for the BD/SUD study and who had at least one parent available to complete the interview about the child were included. We excluded potential probands if they had been adopted or if their nuclear family was not available for study. We excluded any youth with major sensorimotor handicaps that would impede the testing process such as deafness, profound disorders of language such as autism, paralysis, blindness, inadequate command of the English language, or a Full Scale IQ less than 70 as determined by the Wechsler Intelligence Scale for Children (WISC-IV). (29) No other diagnoses were considered in the inclusionary or in the exclusionary criteria. Parents provided written informed consent for their children and children provided written assent to participate. Subjects over the age of 18 provided written informed consent. The human research committee at the Massachusetts General Hospital approved the initial assessments as well as all aspects of both longitudinal studies.

Assessments

All diagnostic assessments were conducted using a clinical interview and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) based structured interviews, by raters with bachelor's or master's degrees in psychology who had been extensively trained and supervised by the senior investigators. Raters were blind to the ascertainment status of the probands. Psychiatric assessments for subjects under 18 years of age relied on the DSM-IV Kiddie Schedule for Affective Disorders-Epidemiologic Version (KSADS-E), (30) and diagnoses were based on independent interviews with the primary caregivers and direct interviews with the probands and siblings if over the age of 12. Psychiatric assessments for subjects 18 or older relied on the Structured Clinical Interview for DSM-IV (SCID). (31) For every diagnosis, information was collected regarding the ages at onset and offset of full syndromatic criteria as well as treatment history.

To assess the reliability of our diagnostic procedures, we computed kappa coefficients of agreement by having three experienced, blinded, board-certified child and adult psychiatrists listen to audiotaped interviews of assessment staff administering the structured diagnostic interview to the subjects. The kappa coefficient was then calculated to measure the diagnostic interrater reliability between the assessment staff and the psychiatrist. Based on 500 assessments from interviews of children and adults who received the same structured interview as described above and who were interviewed by the same group of raters, the median kappa coefficient was 0.98. Kappa coefficients for individual diagnoses included: major depression (1.0), mania (0.95), ADHD (0.88), conduct disorder (CD; 1.0), oppositional defiant disorder (ODD; 0.90), antisocial personality disorder (ASPD; 0.80), and substance use disorder (1.0).

Socioeconomic status (SES) was measured using the Hollingshead Four-Factor Index, with a lower score indicating higher SES.(32)

Measure of Obstetrical, Perinatal, and Infantile difficulties

Mothers were directly questioned regarding the pregnancy, delivery, and infancy difficulties that occurred with each child using a module from the Diagnostic Interview for Children and Adolescents-Parent Version (DICA-P). (33) This module was administered during the structured diagnostic interview completed pertaining to the child's psychiatric history (KSADS-E).

Questions from the DICA-P regarding obstetrical complications included: breech delivery, cesarean section, or other difficulties (e.g. cord around the neck, labor greater than 24 hours). Perinatal difficulties included: placement in an incubator, weight of less than 5 lbs, required hospital stay, and needed surgery. Questions regarding infant behavior included: the need to switch formulas 3 times or more, crying day and night, unusually quiet infant, stiffened infant, floppy infant, and any other issues that seemed unique to the mother, including acting colicky, vomiting, and thrashing about.

Data Analysis

A priori, we excluded any siblings that were older than 18 at their initial visit because probands were between the ages of 4 and 18. No control had any mood disorder and we excluded all siblings with BD (N=41). We assessed differences in demographics between BD probands and non-affected siblings and BD probands and non-mood disordered controls using t-tests for meristic outcomes, the Wilcoxon rank-sum tests for social class (SES), and Pearson χ^2 tests for binary outcomes.

Our analytic strategy was based on two separate comparisons: 1) BD probands versus healthy controls, and 2) BD probands versus non-affected siblings. Primary analyses focused on composite exposures (any obstetrical, perinatal, or infantile difficulties). Secondary, post-hoc analyses looked to examine whether any specific factor accounted for the significant overall findings.

BD probands vs. Controls—Adjusting for age, we used logistic regression to assess the association of obstetrical, perinatal, and infantile difficulties and BD in one model. Additionally, because maternal BD has been shown to be associated with an increase in obstetrical complications (for review, see 34) and because family history of BD is linked with offspring BD, we examined how maternal BD may affect the hypothesized relationships using logistic regression and controlling for age. To test moderation, we tested the interaction between maternal BD and each of the difficulties. To test mediation, we included maternal BD in the original logistic model. From this model, we looked to see whether it reduced or eliminated the effect of each of the difficulties.

BD probands vs. non-affected siblings—We paired BD probands with their non-affected (without BD) siblings and used conditional logistic regression to examine the hypothesized associations. Any BD proband without a sibling was eliminated from the analysis. We paired siblings based on their age; therefore, if probands had more than one sibling, the closest sibling in age to the proband was included. If there was more than one sibling with the same difference in age with the proband, we included the sibling who was subsequently entered into our study after the proband. Diagnoses were defined as any positive response at any assessment. We calculated all statistics using STATA 10.0. All tests were two-tailed, and our alpha level was set at 0.05 a priori. All results are presented as mean ± SD unless otherwise noted.

Demographic Characteristics

The final sample of subjects included 338 children and adolescents, aged 4 to 18 at baseline (12.00 ± 3.37 years). We stratified the sample into three groups (Table 1): healthy controls (N=98), BD probands (N=120), and their non-affected siblings (N=120). Compared to healthy controls, BD probands were more likely to be younger, have a parental history of BD, and have a lifetime history of ADHD and CD. We did not find any significant differences across the groups in sex, mother's age at birth, social class, and parental intactness (all p values > 0.05). Compared to non-affected siblings, BD probands were more likely to be male, and have a lifetime history of ADHD and CD. We did not find any significant differences in baseline age, mother's age at birth, social class, parental intactness, and parental history of BD (all p values > 0.05).

BD probands vs. Controls

While adjusting for age, we found a significant association between BD and infantile difficulties (95% Confidence Interval (CI): 3.00, 14.6; p<0.001). BD subjects were 6.6 times more likely to have experienced an infantile difficulty in childhood compared to controls. We did not find a significant association between obstetrical (Odds Ratio (OR): 1.19; 95 % CI: 0.62, 2.31; p=0.59) nor perinatal difficulties and BD (OR: 0.43; 95% CI: 0.66, 0.85; p=0.10). When we added CD to the model, no association gained or lost significance (infantile difficulties: OR: 5.79; 95% CI: 2.46, 13.6; p<0.001; perinatal complications: OR: 0.99; 95% CI: 0.48, 2.04; p=0.97; obstetrical complications: OR: 0.53; 95% CI: 0.16, 1.68; p=0.28).

During post-hoc analyses, independent of the other infantile difficulties and while adjusting for age, we found that BD subjects were more likely to be a stiffened infant (OR: 7.24; 95%

CI: 1.11, 47.12; p=0.04), and were more likely to experience "other" infantile difficulties (OR: 4.9; 95% CI: 1.27, 18.7; p=0.02) compared to controls. We did not find any significant findings for switching formulas, being a crying infant, a too quiet infant or for being a limp baby (all p values > 0.05).

We then examined how maternal BD may affect the hypothesized relationships. Among mothers with BD (N=11), 9 were from the BD families and 2 were from the control families. When we examined the moderating/interaction effects of maternal BD, we did not find that the associations between any obstetrical, any perinatal, and any infantile difficulties and BD varied by maternal BD history (adjusting for age, all interaction effects p values > 0.05).

When we added maternal BD to the original logistic model, we still found a significant association between infantile difficulties and offspring BD (infantile difficulties: OR: 6.58; 95% CI: 2.99, 14.5; p<0.001; maternal BD: OR: 2.8; 95% CI: 0.55, 14.4; p=0.22). Like the original model, we did not find a significant association for either perinatal (OR: 0.43, 95% CI: 0.15, 1.19; p=0.10) or obstetrical complications (OR: 1.20; 95% CI: 0.62, 2.31; p=0.59). Across all odds ratios, there was less than a 1% change when maternal BD was added to the model.

BD probands vs. Non-affected siblings

When including obstetrical, perinatal, and infantile difficulties in one model, we found that there was a significant association between BD and infantile difficulties. BD probands were 3.3 times more likely to experience infantile difficulties (95% CI: 1.62, 6.56, p=0.001). We did not find a significant associations for either obstetrical (OR: 0.80; 95% CI: 0.39, 1.67; p=0.56) or perinatal complications (OR: 0.73; 95% CI: 0.26, 2.02; p=0.54). When we included CD in the model, no association gained or lost significance (infantile difficulties: 95% CI: 4.3; 95% CI: 1.55, 12.2; p=0.005; obstetrical: OR: 0.74; 95% CI: 0.27, 2.02; p=0.56; perinatal: OR: 0.73; 95% CI: 0.18, 2.93; p=0.66).

In post-hoc analyses, independent of the other infantile difficulties, we found that BD subjects were more likely to have been a stiffened infant (OR: 9.01; 95% CI: 1.00, 81.03; p=0.05) and were more likely to have experienced "other" infantile difficulties (OR: 7.00; 95% CI: 1.53, 32.07; p=0.01). We did not find any significant findings for switching formulas, for being a crying infant, for being a limp baby or for being a too quiet infant (all p values > 0.05).

Discussion

Our current findings partially support our hypotheses by showing significant associations between difficulties during infancy and pediatric BD, especially being a stiffened infant and experiencing other difficulties including acting colicky. Contrary to our hypotheses, we failed to find significant associations between obstetrical or perinatal difficulties and BD. These results were notable for both our comparison groups of BD probands and controls and BD probands and non-affected siblings. We also found that maternal BD did not affect these relationships. These data suggest that experiencing certain infantile difficulties may signal or be related to BD that develops in childhood.

Our positive results linking difficult infant characteristics and BD are in agreement with previous reports. Specifically, we found that BD subjects were more likely to be a stiffened infant (OR: 7.24; p=0.04), and experience "other" infantile difficulties (OR: 4.9; p=0.02) including acting colicky, vomiting, and thrashing about. These results are similar to West et al.'s findings, in which children with pediatric BD were more likely than ADHD children or

controls to have increased difficulty sleeping, nursing, and being consoled as well as acting colicky. (26)

Our results are also reminiscent of previous reports from our group who linked early childhood disinhibition and emotional dysregulation with later BD.(35) Using laboratory-based observations, Hirshfeld-Becker et al. found that children (mean age of 6) with behavioral disinhibition had higher rates of ADHD and mood disorders (11% vs. 3%, p=0.04) or the combination of both (35). The addition of our results to the literature highlights the importance of examining early characteristic in order to identify children at high risk or those who may be targeted for preventive interventions.

Our finding that obstetrical and perinatal complications are not associated with BD is partially supported by the literature. For example, in a meta-analysis across eight predominantly adult samples, Scott et al.(16) did not find an association between obstetrical complications and BD (pooled odds ratio: 1.0, 95% CI: 0.76, 1.35) in comparison to healthy controls. Similarly, using information from the Dublin Psychiatric Case Register and the subject's matched birth records, Browne et al.(36) did not find a greater occurrence or an increased severity of labor and delivery complications compared to matched controls. Further, in more recent research, Singh et al.(37) found that among at-risk children (aged 8 to 17 years) who had at least one parent with BD, there were no significant differences in the amount of prenatal, delivery, and obstetrical complications across children with and without affective, anxiety, and disruptive disorders.

In regards to perinatal complications, Scott et al.(16) did not find a positive association for either low birth weight (pooled odds ratio: 0.91, 95% CI: 0.51, 1.6) or being small for one's gestational age and later BD (pooled odds ratio: 1.79, 95% CI: 0.83, 3.86). Also, among 12–26 year olds in a nested case-control study based on the Danish national register databases, Ogendahl et al.(38) reported no associations between birth weight, birth length, gestational age or the number of previous pregnancies in the mother and BD compared to controls. Finally, among offspring (aged 7–17) of BD parents, Goldstein et al. found that none of the perinatal variables obtained from a medical history questionnaire were associated with offspring BD.(39)

In contrast, Kinney et al.(23) and Pavuluri et al.(40) found positive associations between scores for obstetrical complications and BD. Kinney et al. found that the overall score for obstetrical complications was significantly higher in probands with DSM-III-R BD compared to their siblings without mood disorders ($p<0.002$).(23) Pavuluri et al. found that perinatal factors including birth complications, prolonged labor, and difficult delivery significantly predicted pediatric BD.(40) Also, for every additional perinatal risk factor, the risk for having BD increased six-fold.(40) Differences between our study and these studies could be related to the sample size and the measurement of obstetrical complications. Our sample included 120 BD probands and 120 siblings, whereas Kinney included 30 probands and 25 siblings. Also, Kinney and Pavuluri used a summary score for their measurement of complications while we used binary data.

There are a number of substantial limitations that must be considered when interpreting the results of our paper. The collection of the exposure information is retrospective in nature and may be subject to recall bias. It is possible that mothers of BD children may over-endorse the studied difficulties. However, the young age of our sample and the agreement between maternal retrospective reports of obstetrical complications and medical records that has been previously reported, may reduce the potential recall bias.(41) Our data was collected using the DICA-P, which questions the existence of a problem and does not assess the severity of the problem. Although it captures information regarding a broad range of disorders, it is not

primarily used to assess obstetrical or perinatal complications. Because of the high comorbidity of ADHD and BD, and because of the insufficient number of BD subjects without ADHD that is needed in order to make a meaningful comparison, we did not control for ADHD. Further, information collected on children younger than 12 was collected by the same interviewer that collected diagnostic information. Therefore, these reviewers were not blinded to a child's diagnoses. However, interviewers were still blinded from the ascertainment group of the parent and the hypothesis specific to perinatal, obstetrical, and infantile difficulties. Although extensively trained and supervised, interviewers were not Child and Adolescent Psychiatrists, but held bachelor's and master's degrees in psychology. All interviews were also further reviewed and blinded clinicians determined the final diagnoses.

Despite these limitations, our current data support infantile difficulties as potential prognostic indicators for pediatric BD or as early manifestations of later psychopathology. Our research on obstetrical and perinatal difficulties adds to the current mixed literature for BD subjects. Further research on these difficulties and their relationship to familial and genetic interactions is necessary to lead to a better understanding regarding the etiology and prevention of pediatric BD.

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Table 1

Clinical characteristics of sample (N = 338)

	Healthy controls (n = 98)	Non-affected siblings of BD probands (n = 120)	BD probands (n = 120)
	N (%)	N (%)	N (%)
Sex (% male)	59 (60)	54 (45)[b]	87 (73)
Study of Origin			
Mania	0 (0)	63 (53)	63 (53)
BD/SUD	98 (100)[a]	57 (47)	57 (47)
Parental History of BD	3 (3)[a]	26 (22)	26 (22)
Parental Intactness[*]			
Divorced/Separated	26 (40)	34 (28)	34 (28)
Intact	38 (60)	86 (72)	86 (72)
Conduct Disorder	8 (8)[a]	8 (7)[b]	58 (48)
Attention-Deficit/Hyperactivity Disorder	16 (16)[a]	42 (35)[b]	94 (78)
	Mean ± SD	Mean ± SD	Mean ± SD
Baseline age (years)	13.70 ± 2.10[a]	11.30 ± 3.70	11.30 ± 3.41
Age of mother at offspring	31.60 ± 6.05	30.60 ± 5.04	30.40 ± 5.14
Parental social class	1.77 ± 0.84	1.90 ± 0.96	1.97 ± 1.00

[*] There were 34 missing values for controls (N=64)

[a] Controls vs. BD probands, $p < 0.05$

[b] Non-affected siblings vs. BD probands, $p < 0.05$.

Abbreviations:

BD = bipolar disorder

SUD = substance use disorder

SD = standard deviation

Table 2

Obstetrical, perinatal, and infantile difficulties experienced by subgroup (N = 338)

Difficulties	Healthy controls (n = 98)	Non-affected siblings of BD probands (n = 120)	BD probands (n = 120)
	N (%)	N (%)	N (%)
Obstetrical	56 (57)	78 (65)	79 (66)
Perinatal	13 (13)	16 (13)	17 (14)
Infantile	12 (12)[a]	30 (25)[b]	58 (48)

[a] Controls vs. BD probands, $p < 0.05$.

[b] Non-affected siblings vs. BD probands, $p < 0.05$.

Abbreviations: BD = bipolar disorder.