Original Article

The CBCL predicts DSM bipolar disorder in children: a receiver operating characteristic curve analysis

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Background: No clear consensus has been reached yet on how best to characterize children who suffer from pediatric bipolar disorder (PBD). The CBCL-PBD profile on the Child Behavior Checklist (CBCL) has been consistently reported showing deviant findings on the Attention Problems, Aggressive Behavior, and Anxious-Depressed subscales.

Aim: To examine the sensitivity and specificity of the proposed CBCL-PBD profile for determining DSM diagnosis of PBD.

Methods: We applied receiver operating characteristic (ROC) curve analysis to data from 471 probands from two family studies of attention-deficit hyperactivity disorder and their 410 siblings.

Results: The CBCL-PBD score demonstrated an area under the curve (AUC) of 0.97 for probands and 0.82 for siblings for current diagnosis of PBD, suggesting that the CBCL-PBD provided a highly efficient way of identifying subjects with a current diagnosis of PBD in this sample.

Conclusions: These findings suggest that the CBCL-PBD may provide a highly efficient way of screening for childhood bipolar disorder.

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There is a growing body of literature describing children who show symptoms of affective lability, agitation, aggression, and behavioral dyscontrol. How to best characterize these children and whether to identify them as pediatric bipolar disorder (PBD) has been the focus of considerable study (1–11). The cluster of symptoms that occur in PBD share many, but not all, of the characteristics of late-onset bipolar affective disorder (12), and some modifications of Diagnostic and Statistical Manual (DSM) criteria for pediatric populations (2, 13) have been proposed (14). Despite these diagnostic difficulties, a growing body of literature

suggests that the diagnosis of bipolar disorder in youth is valid (12, 15) and the diagnosis has gained sufficient acceptance for the American Academy of Child and Adolescent Psychiatry to have issued treatment guidelines (2, 3, 7, 9, 10, 13, 14, 16–18).

One of the diagnostic uncertainties in the diagnosis of PBD has been its relationship with attention-deficit hyperactivity disorder (ADHD) given the high comorbidity between the two disorders (5, 10, 18, 19) To address this issue, Biederman et al. (20) described a profile on the Child Behavior Checklist (CBCL; 21) which occurs in children with PBD that is discrete from the CBCL profiles in children without either ADHD or PBD, and more importantly, is different from children with ADHD alone. This profile was subsequently replicated by other groups and confirmed by meta-analysis (22–27). This profile on the

CBCL is characterized by deviance on the Attention Problems, Aggressive Behavior, and Anxious/ Depressed syndrome scales. In contrast, ADHD children without bipolar disorder show deviance largely limited to the Attention Problems scale alone.

In a recent set of studies we used a general population sample of over 21,000 twins to assess the validity of the CBCL-PBD profile (28). We hypothesized that, given the well established high heritability of bipolar disorder (17), the CBCL-PBD profile should be equally heritable. These data showed that the CBCL-PBD profile was highly heritable (54–68%) and had a population prevalence consistent with epidemiologic studies of bipolar disorder (∼1% of boys and girls at ages 7, 10, and 12). Subsequently this phenotype was tested using latent class analysis (LCA) and shown to emerge *a priori* from the data using LCA. The CBCL-PBD latent class was highly heritable and associated with marked increases in suicidal ideation when compared with children who did not fall into this severe class with up to 22% of the children with PBD positive for one of the two suicidal items ('Deliberately harms self or attempts suicide' and 'Talks about killing self') on the maternal report of the CBCL (29).

Kahana et al. (30) extended analysis of the CBCL-PBD profile further by using a multi-informant approach of investigating the relationship between the CBCL, the Teacher Report Form and the Youth Self Report forms of the Achenbach scales. They used logistic regression and receiver operating characteristic (ROC) analysis to evaluate the diagnostic efficiency of the CBCL as a predictor of PBD. They found that the sample of PBD children was significantly different (after adjusting for multiple comparisons) from their 'Any' category of controls on the CBCL on all subscales and differed from children with other disruptive behavior disorders on all scales except Social Problems and Attention Problems. The highest T-scores in PBD children were on the Aggressive, Attention, Anxious/ Depressed, and Delinquent subscales. Although their ROC analyses suggested the CBCL had a high level of predictive validity for PBD (0.81– 0.91), they concluded that the sensitivity and specificity of prediction was too low for clinical use. Unfortunately, they did not evaluate the diagnostic efficiency of the CBCL profile that had been validated by the research review above, which implicated the Attention Problems, Aggression, and Anxious/Depressed subscales. Additionally, to the best of our determination, Kahana et al. did not distinguish between current and lifetime diagnoses of the disorders, a distinction that is critical in the clinical assessment of children.

To address these issues, the present work evaluated the diagnostic efficiency of the CBCL as a predictor of PBD using data from two family studies of ADHD (31, 32). We hypothesized that the attention problems, aggression and anxiety/ depression subscales of the CBCL would allow for accurate determination of PBD status in predicting lifetime and current diagnoses of PBD. Furthermore, because of the known genetic contributions to this disorder (4, 5, 10, 18, 28, 29, 33, 34) we hypothesized that a similar pattern would be seen in siblings of the PBD children.

Methods

Subjects

We studied two groups of boys: 133 ADHD probands and 118 non-ADHD comparisons. Their ages were 10.5 ± 2.9 and 11.6 ± 3.6, respectively. These groups had 126 and 96 siblings, respectively, who provided data. Their ages were 10.7 ± 3.0 and 11.1 ± 2.8, respectively. We also studied two groups of girls: 109 ADHD probands and 111 non-ADHD comparisons (ages 11.1 ± 3.3 and 12.2 ± 3.1, respectively). These groups had 90 and 98 siblings, respectively, who provided data. Their ages were 11.5 ± 3.7 and 11.9 ± 3.4, respectively. All ADHD subjects met full DSM-III-R diagnostic criteria for ADHD at the time of the clinical referral; at the time of recruitment they all had active symptoms of the disorder. Following the guidelines of the Institutional Review Board of the parent institution and in accord with the Helsinki Declaration of 1975, parents gave written informed consent for participation of children and the children participated only if they assented to the study procedures.

The ascertainment procedures were identical for boy and girl probands. We identified psychiatrically referred ADHD probands from lists of consecutive patients from the pediatric psychiatry clinic at the Massachusetts General Hospital. Seventy-seven pediatrically referred ADHD probands were identified from lists of children having evidence of ADHD in the computerized medical record of a Health Maintenance Organization. Within each setting, we selected normal controls from lists of outpatients at pediatric medical clinics.

We selected potential ADHD families if evidence in the medical record and the results of an initial interview suggested a child might have ADHD.

We selected potential control families if evidence in the medical record and the results of an initial interview suggested a child did not have ADHD.

Assessment procedures

We used DSM-III-R-based structured interviews. Psychiatric assessments of youth used the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Epidemiologic Version (Kiddie SADS-E; 35). Diagnoses were based on independent interviews with the mothers and direct interviews with the child. Children younger than 12 years of age (n = 245) were not interviewed directly. To assess childhood diagnoses in the parents, we administered modules from the Kiddie SADS-E. We assessed dimensional measures of psychopathology with the CBCL (21).

Interviewers were blind to the proband's diagnosis and ascertainment site. The direct interviews of mothers and the direct interviews of children were conducted by different raters. When interviewing mothers, the mother's interview about their children was sequenced after the direct interview with the mother about herself in about 90% of families. Raters were trained and supervised by board-certified psychiatrists.

Final diagnostic assignment was made after blind review of all available information by a Diagnostic Committee chaired by Dr Biederman and composed of three board-certified child and adolescent psychiatrists and licensed clinical psychologists. The interviewers were instructed to take extensive notes about the symptoms for each disorder. These notes and the structured interview data were reviewed by the diagnostic committee so that the Committee can make a Best Estimate diagnosis as described by Leckman et al. (36). Definite diagnoses were assigned to subjects who met all diagnostic criteria. Diagnoses presented for review were considered definite only if a consensus is achieved that criteria are met to a degree that would be considered clinically meaningful. By 'clinically meaningful' we mean that the data collected from the structured interview indicated that the diagnosis should be a clinical concern due to the nature of the symptoms, the associated impairment, and the coherence of the clinical picture. To combine discrepant parent and offspring reports, we used the most severe diagnosis from either source as the consensus diagnosis, unless the diagnosticians suspected that the source was not supplying reliable information. Interviewers of subjects were blind to their original ascertainment group (case or control), to all prior data collected from that subject and to his or her family members.

To be given the lifetime diagnosis of BPD, the child had to meet full DSM-III-R criteria for a manic episode with associated impairment. Thus, a child must have met criterion A for a period of *extreme* and persistently elevated, expansive or irritable mood, *plus* criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance, plus criterion C, associated impairment. To be given a current diagnosis of BPD, the child had to meet these criteria within the month prior to the interview.

Statistical analyses

Following the method of Hudziak et al. (28), we defined the CBCL-PBD score as the sum of the three CBCL scales that had been implicated in PBD by the studies reviewed in the Introduction: Attention Problems, Aggressive Behavior, and Anxious/Depressed. We used logistic regression to evaluate the statistical significance of the CBCL-PBD score as a predictor of the BPD diagnosis and used ROC analysis to evaluate the diagnostic efficiency of significant findings.

Receiver operating characteristic analysis assesses the diagnostic efficiency of tests and to adjust cutpoints for clinical or research purposes (37) and has been widely applied to assessing the accuracy of diagnostic tests (38–40). On the ROC graph, the sensitivity (true positive rate) of different cutpoints on the test are graphed on the y-axis along with 1 minus the specificity (the false-positive rate) of the cutpoints on the x-axis to determine the ability of the test to optimize both measures for each point on the test. The higher the graph extends towards the upper left corner of the graph, the higher the discriminatory power of the test.

Receiver operating characteristic analysis summarizes diagnostic efficiency with the area under the curve (AUC) statistic. The AUC ranges from 0.5 (when the test does not predict the disorder in any way) to 1.0 (when the test predicts the disorder perfectly). The AUC has two useful properties. First, it is equivalent to the Mann–Whitney U-statistic computed from a comparison of the CBCL-PBD score between the bipolar disorder and non-bipolar disorder groups (41). Second, it equals the probability that a randomly selected member of the bipolar disorder group will have a more extreme CBCL-PBD score than a randomly selected member of the non-bipolar disorder group (41, 42).

Results

The prevalence of a lifetime history of bipolar disorder was 4.7% (n = 22) for probands and 3.4% (n = 14) for siblings. For current bipolar disorder the prevalence figures were 2.8% (n = 13) and 2.0% (n = 8), respectively. The clinical and familial features of bipolar disorder in these children have been described in prior publications (3). For probands, the mean CBCL-PBD score was 170 ± 26. For siblings it was 158 ± 18.

The logistic regression model predicting lifetime PBD diagnoses from CBCL-PBD scores was significant for both probands ($z = 6.5$, $p < 0.001$) and siblings ($z = 5.9$, $p < 0.001$). These results are shown graphically in the ROC curves in Fig. 1A,B for probands and siblings, respectively. The AUC was 0.89 for probands and 0.85 for siblings suggesting that the CBCL-PBD provided a highly efficient way of identifying subjects with a lifetime history of PBD in this sample. Sensitivity and specificity values at various cutpoints are given in Table 1.
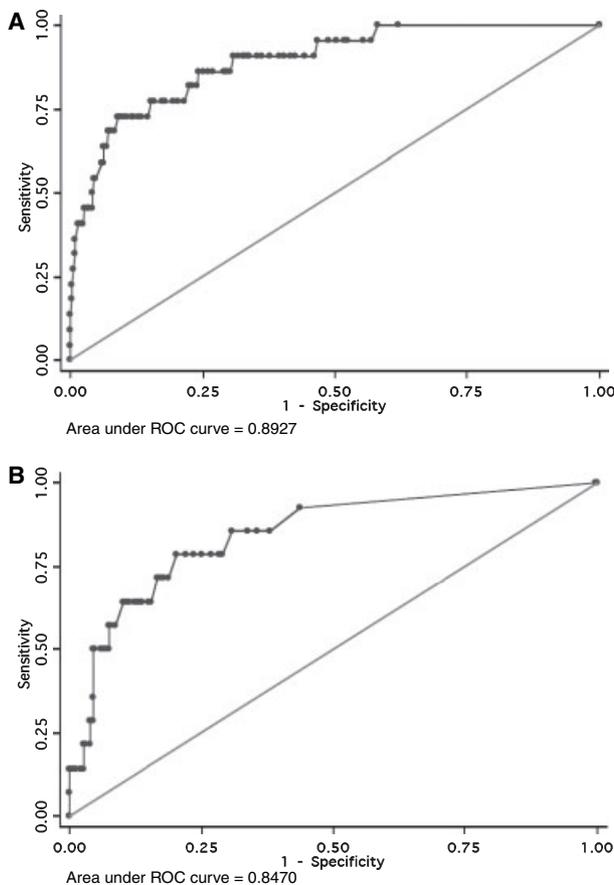
Table 1. Sensitivity, specificity, positive predictive power, and negative predictive power at various cutpoints of the Child Behavior Checklist-pediatric bipolar disorder

Score threshold	Sensitivity	Specificity	Positive predictive power	Negative predictive power
Diagnostic accuracy statistics				
Proband lifetime				
165	91	61	10	99
180	86	74	14	99
195	73	85	20	99
210	64	93	31	98
225	46	97	42	97
240	32	99	70	97
Sibling lifetime				
165	71	83	13	99
180	50	93	19	98
195	21	97	21	97
210	14	98	20	97
225	14	100	67	97
240	14	100	100	97
Proband current				
165	100	60	7	100
180	100	73	10	100
195	100	85	16	100
210	92	93	27	100
225	62	97	33	99
240	46	99	60	99
Sibling current				
165	75	82	8	99
180	50	92	11	99
195	25	97	14	99
210	25	98	20	99
225	25	99	67	99
240	25	100	100	99

Fig. 1. Receiver operating characteristic (ROC) curve for Child Behavior Checklist-pediatric bipolar disorder (CBCL-PBD) in probands (A) with a lifetime diagnosis of PBD (B) and siblings.

The logistic regression model predicting lifetime PBD diagnoses from CBCL-PBD scores was significant for both probands ($z = 5.0$, $p < 0.001$) and siblings ($z = 5.3$, $p < 0.001$). The corresponding ROC curves are given in Fig. 2A,B, respectively. The AUC was 0.97 for probands and 0.82 for siblings suggesting that the CBCL-PBD score was highly efficient for identifying current PBD in both samples.

Discussion

The diagnosis of PBD is a complicated and non-trivial enterprise. It involves careful examination of the child and parental reporting of the child's history. No screening test can substitute for the judgment of well-trained clinicians in making the diagnosis. The results here provide evidence for the utility of a CBCL score based on the attention, aggression, and anxiety/depression subscales to predict structured interview diagnoses of bipolar disorder in children. This value of this score and its potential for generalizability is underscored by the
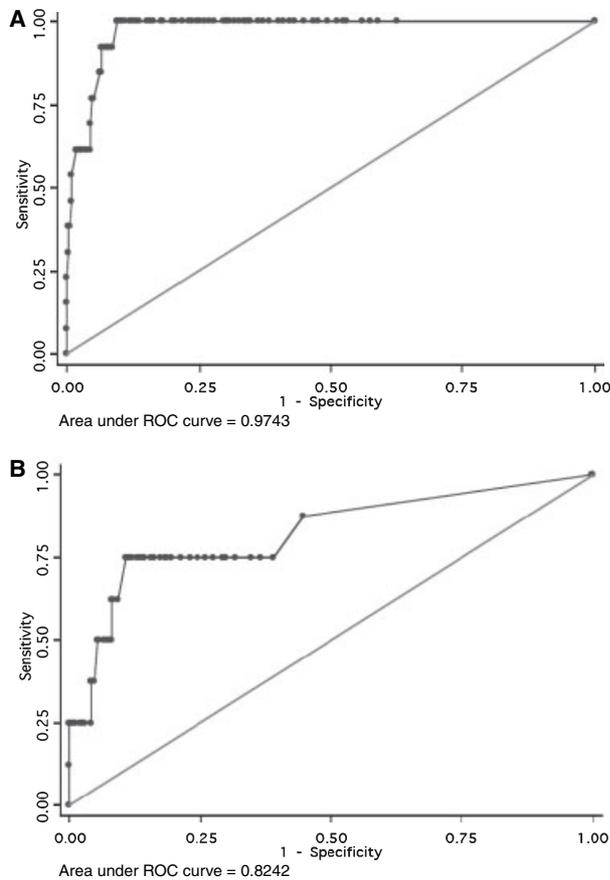
Fig. 2. Receiver operating characteristic (ROC) curve for Child Behavior Checklist-pediatric bipolar disorder (CBCL-PBD) in probands (A) with current diagnosis of PBD (B) and siblings.

fact that the CBCL profile from which it was derived has been replicated across multiple age groups (20, 23–27), multiple treatment settings (inpatient, outpatient), and multiple cultures (American, Dutch, Brazilian, Australian). Notably, as measured by the AUC statistic, the diagnostic efficiency of CBCL predictions of current diagnoses of BPD (0.97) equals the diagnostic efficiency of Troponin-T as a predictor of acute myocardial infarction in an emergency room setting (AUC = 0.94; 43).

There continues to be much debate in the field about the diagnostic definition of PBD (7, 15), which is influenced by clinical traditions, interview methods, and differing interpretations of the nature of a mood episode. In contrast to these diagnostic issues, the CBCL is not affected by clinical tradition, interviewer training, or clinical interpretations. It relies solely on parental answers to questionnaire items. Thus, if it could be shown to be a valid predictor of PBD diagnoses, it would provide clinicians with a useful screening tool and

researchers with an easy method of measuring PBD psychopathology. One can choose cutpoints on the CBCL-PBD to fit the purpose of the clinician or the investigator. For example, if the clinician specifically wants to screen his or her clinical population for PBD and is willing to accept lower specificity, then a higher cutpoint can be used, which would result in higher number of false positives and more children tested. If instead, a researcher would like to investigate whether there is a high percentage of children with PBD in an epidemiological sample and wants to be assured that the children screened will have PBD, a cutpoint can be used, which will result in fewer false positives, but more false negatives.

We conducted our analyses for the ADHD probands and their siblings to correspond to the ascertainment scheme of the original project. These two samples address different issues about the diagnostic accuracy of CBCL-PBD scores for PBD. The proband sample was a mix of ADHD subjects who had been referred to either psychiatric or pediatric clinics. Controls were selected from the same sites. The sibling sample consisted of the siblings of these probands. Thus, we might have expected the diagnostic accuracy of the CBCL-PBD to be greater for the probands because discriminating clinically referred cases is usually easier than cases in the population. Our results showed that this was true for current diagnoses but not for lifetime diagnoses.

We did not find dramatic differences in the AUCs between lifetime and current diagnoses. For siblings, the AUCs for lifetime and current diagnoses were nearly identical (0.85 and 0.82, respectively). For probands, the AUC was somewhat less for lifetime (0.89) compared with current (0.97) diagnoses. Given that the CBCL inquires about behaviors that have occurred in the past 6 months, we would have expected CBCL-PBD scores to be more accurate for current, rather than lifetime, diagnoses. The unexpected accuracy of the CBCL for lifetime diagnoses may be due to the fact that, because PBD is such a severe disorder, children are rarely symptom free for a 6-month period.

Our findings should be evaluated in light of methodological limitations. Although raters administering the structured diagnostic interviews were highly selected, trained, and supervised, they were not clinicians. Although our assessment methods may not elicit the same quality of information as of clinician interviews, in prior work we have shown 90% agreement between expert clinician-derived diagnoses of pediatric BPD and the structured interview diagnoses of non-clinical raters (44). Because our sample had originally been

collected for a family study of ADHD, our findings may not generalize to other populations.

Because our sample was collected through ADHD subjects, it provides an illustration of the ability of the CBCL-PBD score to discriminate bipolar diagnoses but cannot be used to define cutpoints for clinical use. As an illustration of the potential of the method, consider Fig. 2A, which presents results for current diagnoses in probands. Reading from the lower left-hand corner of the plot, each successive point corresponds to an increase of one point of the CBCL-PBD scale. For low scores, sensitivity is very low, which means that few PBD cases would be identified. But because low scores have a low false-positive rate (1– specificity), few false positives are identified. As we climb up the curve from the lower left to upper right corner, sensitivity increases dramatically without a large increase in the false-positive rate. For example, the score with a sensitivity of 75% has a false-positive rate of 10%. Although this false-positive rate is too high for substituting the CBCL-PBD for the PBD diagnosis, it does suggest that the CBCL score could be useful for screening in clinical contexts and as a quantitative trait for research studies.

Despite these limitations, our work suggests that the CBCL-PBD has the potential to be a useful screening instrument for bipolar disorder in children. Specifically, the elevations on the Attention Problems, Aggressive Behavior, and Anxious/ Depressed subscales can be used to create a subscale that is highly heritable and predictive of PBD diagnoses. Our results suggest the efficiency of the measure to predict PBD is somewhat increased if the symptoms of PBD are current rather than lifetime and if the subject had been referred for a psychiatric disorder.

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