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Further Evidence that Severe Scores in the Aggression/Anxiety-Depression/Attention Subscales of Child Behavior Checklist (Severe Dysregulation Profile) Can Screen for Bipolar Disorder Symptomatology: A Conditional Probability Analysis

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Abstract

Background—Previous work shows that children with high scores (2 SD, combined score 210) on the Attention Problems, Aggressive Behavior, and Anxious-Depressed (A-A-A) subscales of the Child Behavior Checklist (CBCL) are more likely than other children to meet criteria for

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Contributors

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All authors contributed to and have approved the final manuscript.

Conflicts of Interest:

Dr. Uchida, Ms. Martelon, Ms. Kenworthy, and Ms. Woodworth have no conflicts of interest to disclose.

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bipolar (BP)-I disorder. However, the utility of this profile as a screening tool has remained unclear.

Methods—We compared 140 patients with pediatric BP-I disorder, 83 with attention deficit hyperactivity disorder (ADHD), and 114 control subjects. We defined the CBCL-Severe Dysregulation profile as an aggregate cutoff score of ≥ 210 on the A-A-A scales. Patients were assessed with structured diagnostic interviews and functional measures.

Results—Patients with BP-I disorder were significantly more likely than both control subjects (Odds Ratio [OR]: 173.2; 95% Confidence Interval [CI], 21.2 to 1413.8; $P < 0.001$) and those with ADHD (OR: 14.6; 95% CI, 6.2 to 34.3; $P < 0.001$) to have a positive CBCL-Severe Dysregulation profile. Receiver Operating Characteristics analyses showed that the area under the curve for this profile comparing children with BP-I disorder against control subjects and those with ADHD was 99% and 85%, respectively. The corresponding positive predictive values for this profile were 99% and 92% with false positive rates of $< 0.2\%$ and 8% for the comparisons with control subjects and patients with ADHD, respectively.

Limitations—Non-clinician raters administered structured diagnostic interviews, and the sample was referred and largely Caucasian.

Conclusions—The CBCL-Severe Dysregulation profile can be useful as a screen for BP-I disorder in children in clinical practice.

Keywords

Mood disorders; severity of illness index; screening instrument; CBCL; bipolar disorder

INTRODUCTION

An emerging pediatric literature documents that pediatric bipolar (BP) disorder is a prevalent and highly morbid disorder. A meta analysis of international epidemiological studies estimated the prevalence of pediatric BP-I and bipolar spectrum disorders to be 1.8% and found no significant difference in prevalence between the United States and other countries (Van Meter et al., 2011).

Although the DSM provides explicit criteria for the diagnosis of BP-I disorder, this is a complex diagnosis that requires high levels of clinical expertise not readily available in clinical practice. This state of affairs calls for easy to use, cost effective methods to aid in the identification of such children in clinical practice. Because of its empirical nature, its excellent psychometric properties and its ease of use as a paper and pencil instrument, the Child Behavior Checklist (CBCL) has been examined as a potential tool to aid in the identification of children at high risk for BP-I disorder (Achenbach, 1991; Mick et al., 2003; Faraone et al., 2005; Hudziak et al., 2005; Althoff et al., 2006).

Several groups have shown that children with a unique profile of the CBCL of high scores (2 SD, combined score ≥ 210) on the Attention Problems, Aggressive Behavior, and Anxious-Depressed (A-A-A) subscales are more likely than other children to meet DSM based diagnoses of BP-I disorder in both epidemiological and clinical samples (Achenbach, 1991; Carlson and Kelly, 1998; Geller et al., 1998; Hazell et al., 1999; Wals et al., 2001;

Mick et al., 2003). This profile has been variedly referred to as the CBCL-pediatric bipolar disorder profile (Biederman et al., 1995), the CBCL – Dysregulation Profile or the CBCL-Severe Dysregulation profile (henceforth referred to as CBCL-Severe Dysregulation profile) (Mick et al., 2003; Althoff et al., 2010). Since the CBCL is rated by parents, it is not influenced by clinical traditions, training, or interpretations, which makes it a particularly compelling screening tool to help identify children at high risk for BP-I disorder

Faraone et al (2005) found that the CBCL-Severe Dysregulation profile was useful for screening both lifetime and current structured interview derived diagnoses of BP-I disorder in youth with attention deficit activity disorder (ADHD) and their siblings. These initial cross sectional findings were followed up by the assessment of the predictive utility of the CBCL-Severe Dysregulation profile in the same sample of children with and without ADHD followed prospectively over an average follow up period of 7.4 years. A positive CBCL-Severe Dysregulation profile at baseline predicted a subsequent diagnosis of BP-I disorder, impaired psychosocial functioning and higher risk for psychiatric hospitalization in children with ADHD without an initial diagnosis of BP-I disorder (Biederman et al., 2009).

On the other hand, other investigators failed to find meaningful associations between the CBCL-Severe Dysregulation profile and a diagnosis of pediatric BP-I disorder (Youngstrom et al., 2005; Volk and Todd, 2007), and others have questioned its validity and specificity (Kahana et al., 2003; Youngstrom et al., 2006; Halperin et al., 2011). These investigators raised questions whether this profile is in fact a measure of mania or bipolar disorder, or of entities such as severe mood disorder or complex comorbidity (hence Severe Dysregulation) (Carlson et al., 2000; Leibenluft et al., 2003). Yet, considering the high morbidity and disability associated with pediatric BP disorder and its unique therapeutic needs, additional research examining the potential utility of the CBCL-Severe Dysregulation profile is warranted. Such knowledge could translate into improved recognition of and therapeutics for children in the community at risk for highly compromised courses and outcomes.

One means of evaluating the utility of the CBCL-Severe Dysregulation profile as a screening tool to help identify children at risk for BP-I disorder is to study its performance in children with a documented diagnosis of BP-I disorder. If the CBCL-Severe Dysregulation profile were to be useful as a screening tool, it should be expected to have a high degree of correspondence with the clinical diagnosis of BP-I disorder and it should be effective in differentiating children with BP-I disorder not only from healthy control subjects but also from those with ADHD. Misdiagnoses of BP-I disorder in children with ADHD and misdiagnoses of ADHD in children with BP-I disorder have been widely reported (Kim and Miklowitz, 2002). Thus, if this profile is found to be useful in distinguish the two disorders, it has potential for clinical implementation.

To address these issues, we examined the ability of the CBCL- Severe Dysregulation profile to discriminate children with a confirmed clinical diagnosis of BP-I disorder from those with ADHD and children with neither of these diagnoses. Based on our previous work, we hypothesized that the CBCL-Severe Dysregulation profile would have good discriminating utility as a screening tool to identify children who might have BP-I from those with ADHD.

METHODS

Subjects

Detailed study methods have been previously described (Wozniak et al., 2012). Briefly, children with BP-I disorder 6 to 17 years of age of both sexes were assessed at the Clinical and Research Program in Pediatric Psychopharmacology at the Massachusetts General Hospital (Wozniak et al., 2005; Wozniak et al., 2010). Comparators were youth of similar age and sex with and without ADHD, without BP-I disorder (Biederman et al., 1992; Biederman et al., 1999; Biederman et al., 2006a; Biederman et al., 2006b). All studies used the same assessment methodology, regardless of the disorder, to classify study patients. We recruited 239 children with BP-I disorder. From 522 families participating in our case control ADHD studies, we randomly selected 162 children with ADHD and 136 control subjects without ADHD, so that the age and sex distribution was similar to that of the patients with BP-I disorder. Patients with and without ADHD with BP-I or major depressive disorders (full or subthreshold) were not included in the present analyses. All study procedures were reviewed and approved by the Institutional Review Board. All subjects' parents or guardians signed written informed consent forms, and children older than 7 years of age signed age appropriate written assent forms.

Ascertainment Method

Potential patients with BP-I disorder were ascertained from our clinical service, referrals from local clinicians or self referral in response to advertisements. Subjects were administered a phone screen reviewing symptoms of DSM-IV BP-I disorder and, if criteria were met, were scheduled for a face to face structured diagnostic interview. In addition to the structured diagnostic interview, an expert clinician (JW) met with each patient with BP-I disorder and his or her parents for a clinical interview to confirm the diagnosis of BP-I disorder. We have published data on the 97% agreement between these clinical interviews with our structured interview diagnosis on the first 69 cases (Wozniak et al., 2003).

Patients with ADHD were identified from referrals to a pediatric psychopharmacology program of a major academic medical center, or from pediatric clinic outpatients of a Health Maintenance Organization (Biederman et al., 1992; Biederman et al., 1999; Wozniak et al., 2010). Control subjects were ascertained from outpatient clinics, referred for routine physical examinations to pediatric medical clinics at each setting, identified from their computerized records as not having ADHD. Screening procedures were similar to those described for the recruitment of the children with bipolar disorder, with the exception that we queried about ADHD (and not bipolar disorder) in the initial telephone screening and each patient was not assessed clinically.

Diagnostic Procedures

Psychiatric assessments of patients were made with the Schedule for Affective Disorders and Schizophrenia for School-Aged Children epidemiologic version (Orvaschel, 1994). Diagnoses were based on interviews with a parent or guardian and with children.

Interviews using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children epidemiologic version were conducted by extensively trained and supervised psychometricians with undergraduate degrees in psychology. This training involved several weeks of instruction of interview mechanics, diagnostic criteria and coding algorithms, observing interviews by experienced clinicians, and being observed while conducting interviews. All diagnoses were reviewed by a signoff committee of board certified child and adolescent psychiatrists or psychologists, who were blind to the patients' ascertainment status, ascertainment site, and data collected from other family members. We computed kappa coefficients of agreement by having experienced clinicians diagnose patients from audiotaped interviews made by the assessment staff. Based on 500 interviews, the median kappa coefficient between raters and clinicians was 0.99 in general, and 0.95 for mania.

Patients were diagnosed with BP-I disorder according to DSM-IV criteria. To ensure that the B criterion symptoms were concurrent with A criterion mood disturbance, patients were directed to focus on the worst or most impairing episode of mood disturbance of at least 1 week, and were assessed whether B criterion symptoms were evident during that time. Also recorded were the onset of 1st episode, the number of episodes, offset of last episode, and total duration of illness. Any child meeting criteria for BP-II or BP-not otherwise specified was not included in this study.

Child Behavior Checklist

The parent (usually the mother) of each participant completed the 1991 version of the CBCL for ages 4 to 18 years. The CBCL queries the parent about the child's behavior in the past six months and aggregates this data into behavioral problem T scores (Achenbach, 1991). A computer program calculates the T scores for each scale. Raw scores are converted to gender and age standardized scores (T scores having a mean of 50 and SD 10). A minimum T score of 50 is assigned to scores that fall at midpoint percentiles of 50 on the syndrome scales to permit comparison of standardized scores across scales. As described previously, the CBCL-Severe Dysregulation profile was defined as positive by a score of 210 (2 SDs) on the sum of the Attention, Aggression, and Anxious/Depressed CBCL scales (Biederman et al., 2009).

Data analysis

Differences in demographics and clinical characteristics were assessed using ANOVA for continuous outcomes, Pearson's chi-square for binary outcomes, and Kruskal Wallis for socioeconomic status (SES). Logistic regression was used to assess the association between each disorder and having scores on the CBCL A-A-A scores of 210 or above. No control subject had A-A-A scores of 210 or above. In order to calculate appropriately, we used a random number generator to choose one control subject to have a score of 210 or above. The subject with the lowest random number was chosen.

We also conducted Receiver Operating Characteristics curve analysis to assess the diagnostic efficiency of the CBCL-Severe Dysregulation profile score as a predictor of BP-I disorder and computed the sensitivity and specificity of the 210 cut point suggested by prior work. Data are expressed as mean $\pm$ SD unless otherwise specified. All tests were two tailed,

and our alpha level was set at 0.05 for all analyses, unless otherwise noted. We calculated all statistics using STATA, version 12.0.

RESULTS

Table 1 shows demographic and clinical characteristics of the sample. There were no differences in the age and sex between groups. The ADHD and BP-I probands had lower SES and the BP-I probands had more racial diversity. Accordingly, all subsequent tests were adjusted for SES and race.

As shown in Figure 1, patients with BP-I disorder were significantly more likely than both control subjects (Odds Ratio (OR): 173.2; 95% Confidence Interval (CI), 21.2 to 1413.8; $P < 0.001$) and children with ADHD (OR: 14.6; 95% CI, 6.2 to 34.3; $P < 0.001$) to have a positive CBCL-Severe Dysregulation profile (A-A-A scores of ≥ 210). Although those with ADHD were also more likely than control subjects to have a positive CBCL-Severe Dysregulation profile, the difference was more modest (OR: 11.9; 95% CI 1.3 to 108.8; $P = 0.03$).

As shown in Figure 2A, the area under the curve (the summary of the diagnostic efficiency) from the ROC analysis was 99% for comparing BP-I probands against Control probands. The CBCL A-A-A score cut point of 210 classified subjects with a positive predictive power of 99% and a false positive rate of less than 0.2%. As shown in Figure 2B, for the comparison with ADHD, the area under the curve was 85% and CBCL A-A-A scores of 210 or above classified subjects with a positive predictive value of 92% and a false positive rate of 8%.

DISCUSSION

Our results provide further evidence for the utility of CBCL-Severe Dysregulation profile as a screening tool for discriminating children with a suspected diagnosis of BP-I disorder from children with ADHD and healthy control children with neither ADHD nor a mood disorder. These results add to an emerging literature documenting the value of this profile as a screening tool, the utility of which has been replicated across multiple age groups, treatment settings (inpatient, outpatient) and cultures (American, Dutch, Brazilian, Australian) (Biederman et al., 1995; Carlson and Kelly, 1998; Geller et al., 1998; Hazell et al., 1999; Wals et al., 2001; Dienes et al., 2002).

Our results showing a positive predictive power of 99% in patients with BP-I disorder versus control subjects, and 92% in those with BP-I disorder versus ADHD suggest that the overwhelming majority of the patients referred for expert diagnosis after scoring positive for the CBCL-Severe Dysregulation profile will be very likely to receive a clinical diagnosis of BP-I disorder. The false positive rates of 0.2% and 8% in each comparison against control subjects and patients with ADHD show that the use of this method will not overwhelm expert clinicians with many false referrals. The areas under the curve of 99% and 85% show that the efficiency of this profile in distinguishing patients with BP-I disorder from control subjects, and children with BP-I disorder from those with ADHD is very good; hence, the CBCL-Severe Dysregulation profile may be useful in addressing the reported common

misdiagnoses of BP-I disorder in children with ADHD and vice versa (Kim and Miklowitz, 2002).

This high positive predictive power comes at the cost of modest sensitivity (57%), which means that the screening procedure will miss nearly half of the BP-I cases. Figure 1A suggests that the cutoff of 210 is quite conservative and we could likely improve sensitivity to about 85% without much loss in positive predictive power by decreasing our cutoff score below 210. Thus, further work should attempt to replicate the value of lower cutoff scores or the inclusion of additional information with the goal of increasing sensitivity while maintaining high positive predictive power.

Our findings are also consistent with our previous work that showed that children with BP-I disorder with a positive CBCL-Severe Dysregulation profile have a robust familiarity with BP-I disorder in 1st degree relatives (Biederman et al., 2013). Our previous work also showed that among the BP-I patients, those with positive CBCL-Severe Dysregulation profiles consistently had more severe correlates of BP-I disorder, including earlier age of onset of BP-I disorder, higher rates of psychiatric hospitalization and higher rates of psychiatric comorbidities (Biederman et al., 2012), indicating that the CBCL-Severe Dysregulation profile may identify children with a particularly severe and dysfunctional form of BP-I disorder (Biederman et al., 2013). Moreover, findings also showed that the overwhelming majority of children with BP-I disorder with a negative CBCL Severe Dysregulation profile had a subsyndromal form of emotional dysregulation, just missing the a priori cutoff point (Biederman et al., 2013). However, the finding that a positive CBCL Severe Dysregulation profile was also associated with ADHD is consistent with prior work showing that a positive CBCL-Severe Dysregulation profile was associated with CBCL measures of post traumatic stress disorder and with diagnoses of major depression and conduct disorder (Ayer et al., 2009; Biederman et al., 2009). These results clearly indicate that the CBCL-Severe Dysregulation profile should only be considered as a useful screening tool for BP-I disorder and not as a replacement for a clinical diagnosis.

No screening test can substitute for the clinical judgment of well-trained clinicians in making the diagnosis. Unfortunately, highly trained child mental health clinicians with expertise in making a diagnosis of BP-I disorder are not widely available in the community, which leaves many children at high risk for serious adverse mental health problems undiagnosed and untreated. Identifying such cases can facilitate appropriate referrals and focus limited societal resources towards a subgroup of children at very high risk for compromised outcomes. Moreover, because the CBCL is not affected by clinical traditions, interviewer training or clinical interpretations, it offers an unbiased approach to identify children at risk for BP disorder and other serious mental health outcomes.

Although Volk et al (2007) failed to find an association between the CBCL-Severe Dysregulation profile and structured interview diagnoses of pediatric BP-I disorder using data from a population based pediatric twin sample, more children with a positive CBCL-Severe Dysregulation profile had oppositional defiant disorder (ODD), conduct disorder (CD), and ADHD and more frequently endorsed suicidal behaviors. These findings are consistent with previous findings showing that ADHD subjects with a positive CBCL-

Severe Dysregulation profile had higher rates of ODD and CD (Kovacs and Pollock, 1995; Biederman et al., 2009). The CBCL-Severe Dysregulation profile in the Volk et al (2007) study was, however, heritable and associated with the number of dopamine transporter (DAT1) 9-repeat 3' untranslated region alleles, a region recently associated with pediatric BP-I disorder (Mick et al., 2008).

Two other studies also failed to find an association between the CBCL-Severe Dysregulation profile and a diagnosis of pediatric BP-I disorder (Youngstrom et al., 2005; McGough et al., 2008). In the negative study by McGough et al (2008), the CBCL-Severe Dysregulation profile was associated with generalized anxiety disorder, ODD, and CD. The negative study by Youngstrom et al (2005) relied on archival data from a large sample from six urban community mental health centers ($n = 3086$) with limited emphasis on operationalized diagnostic algorithms. Thus, differing diagnostic approaches and ascertainment strategies could account for the different findings of studies at various institutions. Nonetheless, more work is needed to help reconcile these discrepant findings.

Our findings need to be viewed in light of some methodological limitations. Although highly selected, trained and supervised, the raters who administered the structured diagnostic interviews were not clinicians. However, we documented very good kappa coefficients of agreement between lay interviewers and expert clinicians (see Methods). Moreover, the diagnosis of BP-I disorder in probands relied on a clinical assessment by an experienced clinician with expertise in pediatric BP-I disorder (JW). Because the sample was referred and largely Caucasian, findings may not generalize to community samples and other ethnic groups.

Despite these limitations, our work suggests that the CBCL-Severe Dysregulation profile has the potential to be a useful screening instrument for identifying children at risk for BP-I disorder and other serious adverse outcomes in the community. While the CBCL remains an attractive tool for screening children at risk for adverse outcomes in clinical settings due to its ease of administration, brevity, and reliability (Achenbach, 1991), we emphasize that clinicians should not use the CBCL Severe Dysregulation to make a diagnosis of bipolar disorder.

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Fig. 1.
Percent of patients per group with CBCL-Severe Dysregulation profile.

A: PATIENTS WITH BP-I DISORDER AGAINST CONTROL **B: PATIENTS WITH BP-I DISORDER AGAINST ADHD** **Fig. 2.**

Receiver Operating Characteristics (ROC) curve analysis: Diagnostic efficiency of the CBCL-Severe Dysregulation profile score as a predictor of BP-I disorder.

Table 1Clinical and Demographic Characteristics ($n = 419$)

	BP-1	ADHD	Control	Statistic
Probands	$n = 140$	$n = 83$	$n = 117$	
Age (years)	10.2 ± 3.0	10.3 ± 2.9	10.5 ± 3.1	$F(2, 337) = 0.4, p = 0.6$
SES	1.8 ± 0.9	1.8 ± 0.8	1.5 ± 0.7	$\chi^2(2) = 10.9, p = 0.01 (**)$
Gender (% male)	104 (74)	66 (80)	90 (77)	$\chi^2(2) = 0.81, p = 0.7$
Past GAF	41.4 ± 5.6	52.8 ± 6.9	72.0 ± 7.5	$F(2, 337) = 680.72, p = 0.001 (***)$
Current GAF	47.1 ± 6.0	57.4 ± 8.4	73.4 ± 7.4	$F(2, 534) = 628.35, p = 0.001 (***)$
Race/Ethnicity				
Caucasian	130 (93%)	83 (100%)	113 (96%)	$\chi^2(6) = 16.9, p = 0.01 (**)$
African-American	2 (1%)	0 (0%)	2 (2%)	
More than 1	8 (6%)	0 (0%)	0 (0%)	
Unknown	0	0 (0%)	0	

Abbreviations: BP-1 = Bipolar-I Disorder; ADHD = Attention Deficit Hyperactivity Disorder; SES = Socioeconomic Status; GAF = Global Assessment of Functioning