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Research report

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 (2SD, 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 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.

1. 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 (2SD, 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

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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.

2. Methods

2.1. Subjects

Detailed study methods have been previously described (Wozniak et al., 2012). Briefly, children with BP-I disorder 6–17 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.

2.2. 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.

2.3. 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.