Prevalence and Genetic Architecture of Child Behavior Checklist–Juvenile Bipolar Disorder

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Background: *No consensus has been reached yet on how best to characterize children with juvenile bipolar disorder (JBD). Several groups have shown that children on the attention problems (AP), aggressive behavior (AGG), and anxious-depressed (AD) syndromes of the Child Behavior Checklist (CBCL) are likely to meet criteria for DSM-JBD. We aimed to use a large population-based twin sample to evaluate the prevalence and genetic architecture of the CBCL-JBD (deviant on AP, AGG, and AD) phenotype and compare these data to children who are deviant on just the CBCL-AP syndrome.*

Methods: *Structural equation modeling (SEM) was applied to CBCL data from 5418, 3562, and 1971 Dutch twin pairs at ages 7, 10, and 12 years.*

Results: *The CBCL-JBD phenotype occurs in ~ 1% of children at each age. Among the children who meet criteria for the CBCL-AP phenotype (~ 5%), between 13 and 20% also meet criteria for CBCL-JBD. The best SEM for CBCL-JBD includes additive genetic, shared and unique environmental factors. The best SEM for CBCL-AP includes dominant and additive genetic and unique environmental factors.*

Conclusions: *These data suggest that CBCL-JBD is common, and even more common among children who have severe attention problems. CBCL-JBD shows familial aggregation due to both genetic and shared environmental factors.*

Key Words: Child, bipolar affective disorder, CBCL, genetic model, ADHD, twin

The existence, prevalence and proper taxonomic designation of juvenile bipolar disorder (JBD) has been the focus of considerable debate. Central to the debate is the fact that little is known about the prevalence of the disorder due to the fact that few epidemiologic studies of JBD have been done (Coyle et al 2003). It has been suggested that the reason that few epidemiologic studies have addressed the prevalence of JBD is due to the fact that there is no agreement on how best to describe children who suffer from JBD. Although the DSM-IV provides explicit criteria for bipolar disorder in adults, experts in the field agree, that these criteria may not be applicable in children and adolescents (Coyle et al 2003; Geller and Luby 1997; Wozniak et al 1995). For a complete review of the debate surrounding the definition of the clinical phenotypes for juvenile mania, please see Leibenluft et al (2003). Carlson et al put it succinctly, "structured interviews provide only so much help" and such children as these, "do not fit the rules of DSM and are 'nosologic orphans' due to problems with the criteria" (Carlson et al 2004). Others point out how important the consideration of comorbidity to juvenile bipolar disorder may be. Tillman et al point out that the onset of attention-deficit hyperactivity disorder (ADHD) before mania and of oppositional defiant disorder (ODD) and conduct disorder (CD) after mania have both clinical and research implications for the study of JBD (Tillman et al 2003). In fact the National Institute of Mental Health (NIMH) Research Round Table on JBD pointed out that the relations between ADHD, ODD, major depressive disorder (MDD) and JBD need to be clarified in order to develop useful taxonomic approaches to this phenotype (Tillman et al 2003; National Institute of Mental Health 2001). There is consensus that standard diagnostic criteria for early onset BPD, that are developmentally appropriate and that exhibit high inter rater reliability and validity must be developed (Geller and Luby 1997; Giedd 2000). As Carlson et al states, the process of refining the DSM was conceptualized as an iterative endeavor and that such a process needs to be considered in the study of JBD (Carlson et al 2004). For such advancement to be achieved, research must move diagnostic processes beyond semantic description of disorder and base them on epidemiologic characteristics and biological processes.

One example of how to study the phenotype of JBD is to do so in relation to ADHD. The ADHD-JBD comorbid phenotype has been the source of considerable study and debate over the past decade (Leibenluft et al 2003). The general phenotype of a child described by this diagnosis is of ADHD with symptoms of aggressive out of control behavior, and affective instability. Although hotly debated, the symptoms of affective instability include manic-like behaviors that cycle rapidly over the course of a day. Definitional artifact makes it difficult to discern whether these symptoms are best described as "manic behaviors" or "severe hyperactivity of ADHD." The interface between ADHD and juvenile bipolar disorder is a complex one, and as a result leads to a great deal of debate on how to best conceptualize children with these symptom domains.

Biederman et al along with several other groups have described a profile on the Child Behavior Checklist (CBCL; Achenbach 1991) which occurs in children with JBD that is discrete from the CBCL profiles in children without either ADHD or JBD, and more importantly, is different from children with ADHD alone (Biederman et al 1995; Wals et al 2001; Carlson and Kelly 1998; Geller et al 1998; Hazell et al 1999; Dienes et al 2002). Figure 1 demonstrates that well children are typically below both the borderline (T score of 65) and clinical (T score of 70) scores for common psychopathologic conditions. Children suffering from JBD have been shown to have a CBCL profile that includes elevation about a T score of 70 on the Attention Problems (AP), Aggressive Behavior (AGG), and Anxious/Depressed (AD) syndromes. In contrast, ADHD children from Biederman's research are best represented by the second profile, one in which the child is elevated on the Attention Problems syndrome alone.

Biederman's work was reported on a sample of children

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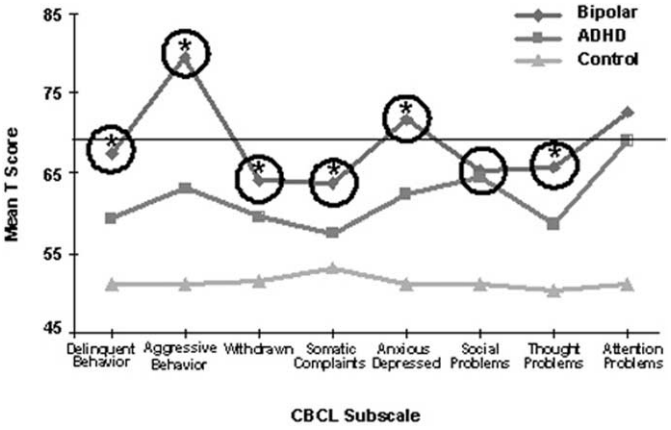

Figure 1. CBCL subscales and their relationship to ADHD and bipolar phenotypes. CBCL, Child Behavior Checklist; ADHD, attention deficit-hyperactivity disorder. * Significantly different between children with bipolar disorder and ADHD versus children with ADHD alone (Biederman et al 1995). Circles indicate subscales also elevated in children of bipolar mothers (Wals et al 2001; Galanter et al 2003).

diagnosed as having JBD using DSM interviews (Biederman et al 1995). A powerful confirmation of the utility of these findings was published by Wals et al who studied children of bipolar mothers (Wals et al 2001). Figure 1 demonstrates that although Biederman was studying children already diagnosed as JBD and Wals et al was studying children of bipolar mothers, the CBCL profile was similar. The utility of this CBCL-JBD phenotype is supported by the work of Carlson and Kelly (Carlson and Kelly 1998) who reported a profile in their sample of inpatients, who were also highly impaired, and appeared to be symptomatically similar to those described by Wals and Biederman. Geller and colleagues (Geller et al 1998) also demonstrated similar findings in their research on children with bipolar disorder. Finally, Galanter et al used this same profile in their work determining treatment response in the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA) study (Galanter et al 2003). In the Galanter study, Diagnostic Interview Schedule for Children (DISC) interview and CBCL data were used to generate a "DISC-MANIA Proxy" and a "CBCL-MANIA Proxy." They report that in expertly diagnosed ADHD children from the MTA study, 10% meet the DISC MANIA Proxy and 11% meet the CBCL-MANIA proxy, and that these two groups were quite similar on their CBCL profiles and nearly identical to the profiles seen in the Biederman, Carlson, Geller, and Wals analyses (Galanter et al 2003). Thus, the CBCL-JBD phenotype has been reported across samples, across countries, and across methodologies (family studies of child bipolar disorder, of ADHD, family studies of children of bipolar mothers). Mick et al's 2003 meta-analysis of the CBCL studies found considerable agreement between research sites indicating the bipolar children are highly aggressive, mixed with depression, and comorbid with ADHD (Mick et al 2003).

The present study sought to shed light on the CBCL-JBD phenotype by estimating its prevalence and its genetic architecture in a large general population twin sample of 7, 10 and 12 year old twins.

Methods and Materials

Subjects and Procedure

The data of the present study are derived from a large ongoing longitudinal study, which examines the genetic and environmental influences on the development of problem behavior in families with 3- to 12-year-old twins. The families are volunteer members of the Netherlands Twin Register, kept by the Department of Biological Psychology at the Free University in Amsterdam (Boomsma et al 2002; Boomsma 1998). Starting in 1987 families with twins were recruited a few months after birth. Currently, 40-50% of all multiple births are registered by the Netherlands Twin Registry. For the present study, we included data of 7, 10, and 12 year old twin pairs. Parents of twins were asked to fill in questionnaires about problem behavior for the eldest and youngest twin at ages 7, 10, and 12 years. After two months a reminder was sent to the nonresponders, and after four months those who still did not respond were telephoned. From ages 3 to 7, and ages 7 to 10 and from 10 to 12 the continued participation was 80%. Families who do not participate at one year (e.g. at age 10) may participate at a subsequent year.

For 822 same sex twin pairs, zygosity was based on blood group polymorphisms (n = 424) or DNA (n = 398). For the remaining twins, zygosity was determined by questionnaire items, filled by the mother, about physical similarity and frequency of confusion of the twins by family and strangers (Goldsmith 1991). The classification of zygosity was based on a discriminant analysis, relating the questionnaire items to zygosity based on blood/DNA typing in a group of same-sex twin pairs. The zygosity was correctly classified by questionnaire in nearly 95% of the cases (Rietveld et al 2000).

A family was excluded when one of the twin pair had a disease or handicap that interfered severely with normal daily functioning (about 2%). Table 1 gives an overview of the number of families with complete twin pairs. An earlier comparison of the parental Socioeconomic Status (SES) distribution with those obtained for the general Dutch population showed a slightly higher frequency of the middle and higher SES-groups (for details see Rietveld et al (2003a). Attrition rates as well as a detailed discussion on the representation of the sample at each age are discussed in detail elsewhere (van Beijsterveldt et al 2003).

Measures

At ages 7, 10, and 12 years problem behavior was measured with the CBCL/4-18 (Achenbach 1991), a questionnaire of 118 items developed to measure problem behavior in 4 to 18 years old children. Again parents were asked to rate the behavior of the child of the preceding 6 months on a 3-point scale.

For the CBCL/4-18 eight syndrome scales were composed according to the 1991 profile (Achenbach 1991). In the present study, subjects with more than three missing items per syndrome were not included in the analyses. This occurred in less than

Table 1. Sample Description (Age, Gender, Zygosity)

	Number of Pairs		
Twin Type	Age 7	Age 10	Age 12
Monozygotic (MZ) Males	905	598	360
Dizygotic (DZ) Males	879	542	308
Monozygotic (MZ) Females	1023	726	410
Dizygotic (DZ) Females	838	538	303
Dizygotic Opposite Sex Male Eldest	927	587	313
Dizygotic Opposite Sex Female Eldest	846	524	277
TOTAL	5418	3515	1971