Shared Environmental Contributions to the CBCL-Bipolar Phenotype in Dutch Twins

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Introduction

The existence, prevalence and proper taxonomic designation of the comorbid condition, ADHD with bipolar disorder, has been the source of considerable attention 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 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 ADHD". In any event, these children do exist, and how best to describe them remains unclear.

Many prior investigations of Bipolar-ADHD children (Biederman et al., 1995) and children of bipolar mothers (Wals et al., 2001) yield a profile on the Child Behavior Checklist (CBCL) that includes elevation about a T score of 70 on the Attention Problems (AP), Aggressive Behavior (AGG) and Anxious/Depressed (A-D) syndromes of the CBCL. Carlson and Kelly (Carlson and Kelly, 1998) reported a profile consistent with these reports 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 her research on children with bipolar disorder.

Objective

To determine the prevalence and genetic architecture of the CBCL-Bipolar phenotype (AP/AGG/A-D) in general population samples of twins at ages 7, 10, and 12.

Questions

1) What percentage of children deviant on CBCL-AP also meet the criteria for the extreme CBCL-Bipolar phenotype?
2) What are the genetic and environmental contributions to this phenotype?
3) Do genetic models suggest that CBCL-Bipolar is an extreme variant of CBCL-AP only?

Sample

Mother report CBCL data for Dutch twin pairs at ages 7, 10, and 12

Twin Type	Number of Participants		
	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 (DOS M_F)	927	587	313
Dizygotic Opposite Sex female eldest (DOS F_M)	846	524	277
TOTAL	5418	3515	1971

Measures

- The CBCL (Achenbach, 1991) was used to measure eight behavioral and emotional syndromes.
- Three syndrome scores known to distinguish between problems with attention only and Bipolar-ADHD were selected - Attention Problems (AP), Aggressive Behavior (AGG), and Anxious/Depressed (A-D).
- Deviance was defined as having a T-Score greater than 70 on a subscale
- A "CBCL-Bipolar" score was created using the sum of scores on AP, AGG, and A-D.

Data Analyses

- Deviance on the three subscales were computed using Dutch normative data. Frequencies were then computed using SPSS.
- Means, variances, and twin correlations were calculated using the statistical software program Mx and are presented below. Differences in mean scores were tested by likelihood-ratio x^2-tests. Because the CBCL-Bipolar score was not normally distributed, the data was square-root transformed to approximate normal distribution before analysis. Transformed scores were used in the correlation and structural equation modelling.
- All model fitting was performed on transformed data with Mx. The basic model was an ACE or ADE model with and without sex and interaction effects. The possible presence of an interaction component was tested by equating the variances between MZ and DZ twins. The basic model is shown below.
- The significance of the A, D, and C factors or sibling interaction was tested by dropping these variance components, using the x^2- difference test. We also computed likelihood-based 95% confidence intervals.

mz=1, dz=.5   mz=1, dz=.25

CBCL-Bipolar or AP P1   ←→ i CBCL-Bipolar or AP P2
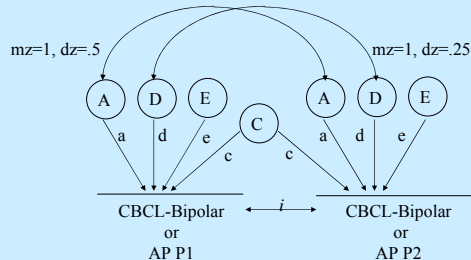
Results

The prevalence of the AP only phenotype at all ages was between 4.1 – 6.6% of twin pairs. The prevalence of the AP/AGG/A-D phenotype was approximately 1% at all ages. Of the AP children, depending on age and sex, between 13.5 – 25.8% of those also met criteria for the AP/AGG/A-D phenotype (see Tables below).

Frequency of CBCL-AP and CBCL-Bipolar phenotype by age and sex

Age	Male		Female	
	CBCL-AP	CBCL-Bipolar	CBCL-AP	CBCL-Bipolar
7	4.8%	0.8%	5.6%	0.8%
10	4.1%	0.9%	5.2%	0.9%
12	4.6%	1.2%	6.6%	0.9%

Percentage of children with CBCL-AP who also meet criteria for CBCL-Bipolar

Age	Male	Female
7	16.7%	14.2%
10	23.0%	17.3%
12	25.8%	13.5%

Model Fitting Results

The MZ correlations were greater than two times the DZ correlation, suggesting the possibility of genetic dominance (or interaction) for CBCL-AP. This was not true for CBCL-Bipolar (see Tables below). An ACE model, either with or without sex information, depending on the age at which the sample was taken, fit the CBCL-Bipolar data best, while dominance was evident in the AP phenotype, as has been seen elsewhere. All of the model fitting results could not be shown below, but are available for review in the documents below the poster. Model estimates for the best fitting models are shown below.

Twin-Twin Correlations, CBCL-AP Phenotype

Age	Twin Type	Male	Female
7	MZ	.729	.720
	DZ	.233	.275
	DOS	.261 (M_F)	.333 (F_M)
10	MZ	.716	.731
	DZ	.217	.218
	DOS	.282 (M_F)	.293 (F_M)
12	MZ	.688	.711
	DZ	.203	.288
	DOS	.246 (M_F)	.195 (F_M)

Twin-Twin Correlations, CBCL-Bipolar Phenotype

Age	Twin Type	Male	Female
7	MZ	.852	.827
	DZ	.490	.530
	DOS	.487 (M_F)	.516 (F_M)
10	MZ	.821	.793
	DZ	.470	.493
	DOS	.458 (M_F)	.496 (F_M)
12	MZ	.822	.813
	DZ	.418	.505
	DOS	.463 (M_F)	.471(F_M)

Model Estimates

CBCL-AP Phenotype

	Male				Female			
Age	A	C	D	E	A	C	D	E
7	.60	-	.14	.27	.60	-	.14	.27
10	.60	-	.13	.27	.60	-	.12	.28
12	.61	-	.09	.30	.54	-	.18	.28

CBCL-Bipolar Phenotype

	Male				Female			
Age	A	C	D	E	A	C	D	E
7	.59	.27	-	.15	.59	.27	-	.15
10	.68	.18	-	.14	.57	.26	-	.17
12	.77	.07	-	.16	.64	.17	-	.19

Summary of Model Fitting

Model fitting revealed different genetic architecture for the AP only versus the complex phenotype. An ACE model (either with or without sex information, depending on the age at which the sample was taken) fit these data best, while dominance (or interaction) was evident in the CBCL-AP phenotype, as has been seen elsewhere. There were sex differences at ages 10 and 12, but these were not seen at age 7, nor were they extreme at the older ages.

This argues against the CBCL-Bipolar phenotype being the more extreme version of the CBCL-AP phenotype. The magnitude of the C contribution in the CBCL-Bipolar phenotype ranges from 7 to 27%, with the highest estimates being seen in the children at age 7.

Discussion

The findings that up to 25% of the children with CBCL-AP also meet the criteria for CBCL-Bipolar may help explain why rates of the complex phenotype are reported to be so much higher in ADHD clinics than in general pediatric settings. In other words, if one starts with an ADHD population, the complex phenotype occurs in many of those children. Additionally, findings that there is a different genetic architecture for the CBCL-Bipolar phenotype suggests that it is less likely to be an "extreme version" of the AP phenotype.

Finally, the findings of a shared environmental component to the expression of the CBCL-Bipolar phenotype is fascinating. Thus far, most other models have shown the transmission of Bipolar disorder to be either genetic or of the unique environmental type. While a significant genetic component is seen in these data, the finding of a shared environmental component, especially in the young, suggests a possibility of a modifiable factor in the expression of this extreme phenotype. More research into characterizing this component seems warranted.

Limitations

1. Participants could be enrolled in the NTR and followed for a number of years. Thus, the 12 year old and 10 year old samples are subsets of the 7 year old sample. When enough children have reached the age of 12, these will be able to be placed into a fully longitudinal design, but this is not yet possible.
2. Data on maternal report may not generalize to other informants. Our group is currently collecting data on older twins by father and teacher report in order to test for these factors.
3. We did not directly interview the parents or children in this study and therefore cannot present data on the number of children who would meet criteria for DSM-IV Bipolar Affective Disorder.
4. Data in this report are limited to children up to the age of 12. Because the expression of Bipolar Affective Disorder is often in late adolescence or early adulthood, these data and the estimates of heritability resulting would apply best to childhood bipolar disorder.

Conclusions

- Between 13 and 26 percent of children who meet at deviance on CBCL-AP also meet deviance on the extreme CBCL-Bipolar phenotype.
- CBCL-AP is influenced by genetic factors that are both dominant and additive, while the CBCL-Bipolar phenotype is influenced by additive genetic and shared environmental factors.
- The CBCL-Bipolar is less likely to be an extreme version of CBCL-AP, given different genetic architecture.

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