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Manic Symptoms and Behavioral Dysregulation in Youth with Velocardiofacial Syndrome (22q11.2 Deletion Syndrome)

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ABSTRACT

Mania and bipolar disorder have been reported in adolescents and adults with velocardiofacial syndrome (VCFS; also known as 22q11.2 deletion syndrome). Children with VCFS have a high prevalence of attention-deficit/hyperactivity disorder (ADHD), which may constitute a risk factor for the eventual development of bipolar disorder in this population. Therefore, we sought to determine whether children with VCFS exhibit more manic symptoms than community controls that also may have learning disorders and ADHD. The study population consisted of 86 children with VCFS and 36 community controls from ages 9 to 15 years, using measures of Young Mania Rating Scale–Parent Version, Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL), Child Behavior Checklist (CBCL), and Wechsler Intelligence Scale for Children–3rd edition (WISC-III). The results indicate that manic symptoms were not more prevalent in VCFS than in a community sample of children with learning disorders and ADHD. However, after accounting for symptoms of depression and ADHD, we found that manic symptoms in VCFS predicted uniquely to scores on four Child Behavior Checklist (CBCL) subscales, including anxiety, somatization, thought, and conduct problems. In contrast, manic symptoms in controls predicted uniquely to conduct problems only. Accordingly, our findings of severe behavioral impairment in youth with VCFS and manic symptoms suggest that these children may warrant more intensive monitoring and treatment relative to youth with VCFS and ADHD only.

INTRODUCTION

VELOCARDIOFACIAL SYNDROME (VCFS), also known as 22q11.2 deletion syndrome, Di-George syndrome, and conotruncal anomalies face syndrome, is a multiple anomaly disorder that is caused by a microdeletion of DNA from chromosome 22 at the q11.2 band (Driscoll et al. 1992). Individuals with VCFS exhibit a highly variable phenotype (Robin and Shprintzen 2005). Physical phenotypes include palate, heart, renal, vascular, limb, brain, spine, and immunologic anomalies (Robin and Shprintzen 2005). Language and motor delay occur in

nearly all cases (Shprintzen 2000). Mild mental retardation, persistent coordination deficits, and poor academic performance are also common. The deletion at chromosome 22q11.2 is also associated with a high frequency of behavioral disorders during childhood, including attention-deficit/hyperactivity disorder (ADHD), specific phobias, and major depressive disorder (MDD; Goldberg et al. 1993; Pulver et al. 1994; Karayiorgou et al. 1995; Papolos et al. 1996; McCandless et al. 1998; Gothelf et al. 1999; Arnold et al. 2001; Feinstein et al. 2002; Antshel et al. 2006). There is some evidence, however, to suggest that the prevalence rates of several of these psychiatric disorders in children with VCFS do not differ significantly from cognitively matched samples (Feinstein et al. 2002).

As children with VCFS move into adulthood, several groups report high rates of schizophrenia (Murphy and Owen 1997; Bassett et al. 1999; Murphy et al. 1999; Arnold et al. 2001; Pinquier et al. 2001; Feinstein et al. 2002). Less commonly reported is bipolar mood disorder (Papolos et al. 1996). Despite relatively few research reports of bipolar disorder in adults with VCFS, however, we are aware of many anecdotal reports of mania and bipolar disorder in children with VCFS. This discrepancy might be due to the natural course of VCFS psychiatric phenotype. In fact, the oldest patients in the study by Papolos and colleagues had schizophrenia and schizoaffective disorder, suggesting that the nature and course of psychiatric illness in VCFS patients is still not clear (Papolos et al. 1996).

Papolos and colleagues found that 64% of patients with VCFS met *Diagnostic and Statistical Manual for Mental Disorders*, 3rd edition, revised (DSM-III-R; American Psychiatric Association 1987) criteria for a spectrum of bipolar disorders with full syndromal onset in late childhood or early adolescence [mean age of onset = 12 years, standard deviation (SD) = 3] (Papolos et al. 1996). In addition, 20% of children with bipolar disorder met DSM-III-R criteria for ADHD, whereas 16% met criteria for DSM-III-R attention-deficit disorder without hyperactivity. These findings suggest an unusually strong association between VCFS and early-onset bipolar disorder. The high comorbidity between ADHD and bipolar disorder is consistent with other studies of bipolar youth

(Biederman et al. 1996) and the familial association between the two disorders (Faraone et al. 2003; Faraone and Tsuang 2003).

As noted above, the most common psychiatric co-morbidity in children and adolescents with VCFS is ADHD as found in 35–55% of the cohort (Papolos et al. 1996; Arnold et al. 2001; Feinstein et al. 2002; Antshel et al. 2006). In light of the high incidence of ADHD in VCFS, the frequent association between ADHD and bipolar disorder, and the potential risk for early onset bipolar disorder in children with VCFS, we were interested in whether children with VCFS exhibit manic symptoms to a greater extent than typically developing controls, and whether manic symptoms in children with VCFS was associated with a distinctive behavioral phenotype relative to our control sample.

There have been few systematic studies of the overlap between ADHD and bipolar disorder due to the prevailing skepticism about the very existence of childhood bipolar disease (Goodwin and Jamison 1990) and the clinical difficulties in distinguishing ADHD from mania in children due, in part, to the overlap in symptoms (Carlson 1984) and to the finding that childhood mania may present differently from its adult counterpart (Davis 1979; McGlashan 1988; Biederman et al. 1995). Nonetheless, Biederman and colleagues (1995) described a Child Behavior Checklist Pediatric Bipolar Disorder (CBCL-PBD) profile that discriminated children with bipolar disorder (many of whom also had ADHD) from ADHD children who did not have bipolar disorder. The profile accurately discriminated bipolar from nonbipolar children (Faraone et al. 2005). Similarly, other investigators have found that the CBCL separates bipolar from ADHD groups (Geller et al. 1998; Hazell et al. 1999).

Insofar as these findings suggest that childhood mania is distinguishable from childhood ADHD, the present work sought to investigate the extent to which manic symptoms accounted for behavioral problems after accounting for the effects of symptoms of ADHD and depression. On the basis of this prior literature, we tested two hypotheses: (1) Children with VCFS would display more manic symptoms than community controls, and (2) in children with VCFS (but not necessarily community controls), after

accounting for the variance explained by symptoms of ADHD and depression, the presence of manic symptoms (based on the Young Mania Rating Scale–Parent Version), would account for a significant portion of variance in scores on the Anxiety, Social Problems, Thought Problems, and Aggression subscales of the CBCL.

METHODS

Participants

The study population consisted of 86 children with VCFS (39 females; mean age = 11.9, SD = 2.1) and 36 community controls (12 females; mean age = 12.0; SD = 1.9). All children ranged in age from 9 to 15 years. Children with VCFS were recruited from the Center for the Diagnosis, Treatment, and Study of VCFS at SUNY–Upstate Medical University. All children with VCFS had a fluorescent in situ hybridization (FISH)-confirmed deletion in the chromosome 22q11.2 region. Community controls were recruited from a local public school district. Because children with VCFS exhibit learning disabilities and ADHD, we did not exclude the presence of either learning disabilities (LD) or ADHD from our control sample. In addition, we specifically excluded children whose parents reported were in gifted classes, earned all "As", or read before the age of five. This resulted in a control sample in which LD and ADHD were over-represented relative to the general population. We reasoned that this strategy would enable us to account for variance due to LD/ADHD in general as opposed to variance due to VCFS per se. Children with an identifiable neurological condition other than VCFS (e.g., traumatic brain injury, seizure disorder, birth weight below 2,500 grams as reported by parent) that is known to affect cognitive or neuropsychiatric function were excluded from participation from both groups. Informed consent/assent was obtained from parents and children under protocols approved by the institutional review board.

Measures

Young Mania Rating Scale–Parent Version (YMRS): This is an 11-item scale in a Likert-scale format. Items describe symptoms that are generally associated with mania, and parents are asked to choose the most appropriate description of their child. Comparisons between parent ratings on this scale and clinical ratings based on standard psychiatric interviews indicate that the scale has adequate discriminative validity (Gracious et al. 2002). We used the summary score of the YMRS-P as a continuous variable in our statistical analyses.

Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL): The K-SADS-PL is a semi-structured diagnostic interview schedule that provides *Diagnostic of Statistical Manual of Mental Disorders*, 4th edition (DSM-IV; American Psychiatric Association 1994) psychiatric diagnoses, based on interviews with the child's primary caregiver (almost always his/her mother) and the child (Kaufman et al. 1997). Although we made every attempt to interview the child as well as the parent, the child often had difficulty responding; in these cases, the K-SADS-PL data was based on the parent's response. A child psychiatrist or clinical child psychologist administered the K-SADS-PL. Interrater reliability, based on 12 interviews, was calculated with the kappa coefficient, and was 0.91. The psychiatric status of this sample, based on the analysis of the K-SADS-PL, has been described in Antshel et al. (2006).

For the current report, we used K-SADS-PL responses to develop dimensional scores for depression and ADHD, which we entered into our regression model. The K-SADS-PL consists of both an extensive screening module and five supplemental modules. The screening module contains DSM-IV symptoms for each specific diagnostic category. The interviewer assigns scores for each symptom, indicating whether the symptom is present, absent, or present but at the subthreshold level. Generally, subthreshold symptoms are assigned when the child is experiencing the symptom, but at a less frequent or less intense level than would warrant a threshold-level score. Because many children with VCFS are at risk for psychiatric disorders, but are not necessarily exhibiting all the symptoms that would warrant a definite diagnosis, we were interested in identifying children whose parents reported

either subthreshold- or threshold-level symptoms of depression or ADHD.

We used the depression and the ADHD screening modules to develop dimensional scores based on this instrument. For each screening module, we assigned scores of 1 for each symptom item that was not present; scores of 2 for each subthreshold-level symptom that was endorsed, and scores of 3 for each threshold-level symptom that was endorsed. Then we summed all the scores, thereby deriving a dimensional score for depression and for ADHD. These scores were entered into our regression model, as described below.

Child Behavior Checklist (CBCL): Parents were asked to complete the CBCL, a widely used and reliable scale consisting of 113 items (Achenbach 1991). We compared subscale scores and a CBCL-PBD score between study groups. To derive the CBCL-PBD scores, following the guidelines of Faraone and colleagues (2005), we summed the scaled scores for anxiety, depression, attention and aggression.

Wechsler Intelligence Scale for Children–3rd edition (WISC-III): The WISC-III is comprised of 13 subtests (Wechsler 1991). The current analyses only utilized the general measure of intellectual functioning, the Full Scale IQ (FSIQ).

Wechsler Individual Achievement Test–2nd edition (WIAT-II): The WIAT-II (Wechsler 2001) is an individually administered test of academic achievement, which has been standardized with 4,252 children in grades K–12. This test contains nine subtests, which are aggregated into four composite scores: Reading, mathematics, language, writing, and an omnibus total score (M = 100, SD = 15). For the present analyses, only the total scores were used. These total scores were used to operationalize a learning disability. A designation of learning disability was based on a 1.5 S.D. discrepancy between the FSIQ of the WISC-III and the WIAT-II total score or a WIAT-II total score of < 85.

Statistical analyses

Univariate and Chi-square analyses were conducted to compare the study groups on intelligence quotient (IQ) scores, gender ratio, socioeconomic status (SES), and presence of learning disabilities. Univariate analyses were conducted to determine if study groups differed in scores on the YMRS-P and the CBCL-PBD profile. A multivariate analysis of variance (MANOVA) was conducted to compare CBCL subscale scores between participants with VCFS and controls. A stepwise regression model was used to determine the degree to which manic symptoms (based on the summary score of the YMRS-P) were predictive of subscale scores on the CBCL, after controlling for the variance accounted for by the presence of symptoms of depression and ADHD (based on K-SADS dimensional scores). The three predictors (symptoms of mania, depression, and ADHD) were entered into the model as a block, using the stepwise command. (Prior to the regression analyses, initial linear regressions were conducted to determine the extent to which FSIQ, SES, and age were significant predictors of CBCL subscale scores. The significant predictors were entered as the first step in the stepwise regression model.)

RESULTS

As shown in Table 1, study groups did not differ in either age [$F(1, 121) = 0.022$; $p = 0.88$, or gender-ratios, $\chi^2 = 1.51$; $p = 0.22$]. Socioeconomic status was significantly lower in the control group [$F(1, 99) = 4.39$; $p = 0.04$], and FSIQ was significantly lower in the children with VCFS [$F(1, 121) = 84.21$; $p < 0.001$, $\eta^2 = 0.41$]. As noted above, K-SADS-PL–based diagnoses of study participants have been described elsewhere.

The omnibus MANOVA on the CBCL scales was significant [Wilks $\lambda = 0.765$, $F(11, 103) = 2.87$, $p = 0.002$, $\eta^2 = 0.24$]. Follow-up univariate analyses revealed that the two groups differed on several CBCL subscales, including Somatic Complaints [$F(1, 120) = 5.63$, $p = 0.019$, $\eta^2 = 0.05$], Social Problems [$F(1, 120) = 11.58$, $p = 0.001$, $\eta^2 = 0.09$], Thought Problems [$F(1, 120) = 6.56$, $p = 0.012$, $\eta^2 = 0.06$]. Across all subscales, parents of children with VCFS rated their child as having more behavioral difficulties. (See Table 1 for complete group mean scores.)

Because the study groups differed in SES and FSIQ, both variables were entered as covariates in the analysis of group differences in

TABLE 1. DESCRIPTIVE DATA

	VCFS (n = 86)	Control (n = 36)
Age	11.9 (2.1)	11.9 (1.9)
Sex (%male)	55	67
Socioeconomic status	47.5 (12.5)[a]	41.6 (13.8)
Participants taking medication (%)	34	31
Antidepressants (% of sample)	4.6	5.5
Mood stabilizers	6.0	5.5
Stimulants/atomoxetine	18.6	19.4
Atypical antipsychotics	3.4	0
WISC-III Full Scale IQ	70.5 (13.2)[b]	94.8 (13.7)
Incidence of learning disabilities	63 (75%)[b]	14 (37.8%)
YMRS Summary Score	8.0 (8.1)	7.0 (6.1)
CBCL Anxiety T score	60.8 (8.8)	58.9 (8.8)
CBCL Depression T score	61.9 (9.0)	59.7 (11.3)
CBCL Somatic Complaints T score	62.2 (9.6)[c]	57.7 (8.7)
CBCL Social Problems T score	65.9 (9.2)[b]	59.4 (10.1)
CBCL Thought Problems T score	63.4 (9.4)[a]	58.6 (8.9)
CBCL Attention Problems T score	65.9 (8.9)	62.8 (12.4)
CBCL Rule-Breaking T score	57.3 (7.1)	54.7 (7.0)
CBCL Aggression T score	60.0 (9.6)	56.9 (8.3)
CBCL Internalizing T score	62.6 (10.0)[c]	56.0 (14.0)
CBCL Externalizing T score	57.7 (9.7)[a]	53.0 (9.9)
CBCL Total T score	63.7 (8.4)[b]	56.8 (11.8)

Socioeconomic status was measured by the Hollingshead (1975) scale.

VCFS = Velocardiofacial syndrome; WISC-III = Wechsler Intelligence Scale for Children–3rd edition (Wechsler, 1991); YMRS = Young Mania Rating Scale–Parent Version (Gracious et al., 2002); CBCL = Child Behavior Checklist (Achenbach, 1991).

[a] $p < 0.05$.
[b] $p < 0.001$.
[c] $p < 0.01$.

YMRS-P scores. This analysis indicated that groups did not differ in number of manic symptoms, on the basis of scores on the YMRS-P [$F(1, 113) = 0.09$; $p = 0.77$; $\eta^2 = 0.01$]. Similarly, although scores on the CBCL-PBD profile tended to be higher for the VCFS sample than those of controls [$F(1,113) = 3.08$; $p = 0.08$; $\eta^2 = 0.03$], differences were negligible once SES and FSIQ were entered as co-variates [$F(1,113) = 0.00$; $p = 1.0$].

The results of stepwise regression analyses on CBCL subscale scores are reported in Tables 2 and 3. Prior to conducting stepwise regression analyses, simple linear regressions were conducted to determine the extent to which FSIQ, SES, and age were significant predictors of CBCL subscale scores. SES was not a significant predictor of CBCL scores for either group. Age was a significant predictor of depression in children with VCFS, but not controls. FSIQ was a significant predictor of social and thought problems in controls, but not in children with VCFS. Accordingly, for children with VCFS, age was entered in the first block of predictors of CBCL–Depression. Similarly, for controls, FSIQ was entered in the first block of predictors of CBCL–Social Problems and CBCL–Thought Problems.

In children with VCFS, the presence of manic symptoms was the only significant predictor of CBCL subscale scores on anxiety (accounting for 9.5% of the variance), somatization (10%), thought problems (23%), and rule breaking (23%). Both manic and ADHD symptoms were significant predictors of scores on social problems (accounting for 21% and 8% of the variance, respectively) and attention (11% and 12.7% of variance, respectively). Manic, ADHD, and depression symptoms all were significant predictors of scores on aggression. Manic symptoms accounted for over 30% of the variance in scores on aggression. Depression and ADHD symptoms accounted for only 5% and 4% of the variance, respectively.

In our sample of community controls, the presence of manic symptoms was the only significant predictor of CBCL subscale scores rule breaking (accounting for 20%). FSIQ and manic symptoms were predictors of scores on social problems, accounting for 15% and 11% of the variance, respectively. Both manic and ADHD symptoms were significant predictors of scores on anxiety (accounting for 21% and 11% of the variance, respectively). Both manic and depression symptoms were significant predictors of somatization (accounting for 9% and 24% of the variance, respectively) and aggression (31% and 13% of variance, respectively). FSIQ as well as manic, ADHD, and depression symptoms were significant predictors of scores on thought

TABLE 2. SIGNIFICANT PREDICTORS OF CBCL SUBSCALES IN VCFS SAMPLE FROM SCORES ON YMRS AND DIMENSIONAL SCORES OF DEPRESSION AND ADHD FROM K-SADS-PL

Subscales	Age/symptom predictors	Beta	T score	P value	R^2 change
Anxiety	Mania	0.31	2.77	0.007	0.095
Depression	Age	0.25	2.22	0.03	0.161
	Depression	0.32	2.80	0.007	0.082
Somatization	Mania	0.32	2.86	0.006	0.101
Social Problems	Mania	0.45	4.59	0.000	0.213
	ADHD	0.29	2.91	0.005	0.083
Thought Problems	Mania	0.48	4.70	0.000	0.232
Attention	ADHD	0.35	3.39	0.001	0.127
	Mania	0.34	3.27	0.002	0.113
Rule Breaking	Mania	0.48	4.71	0.000	0.233
Aggression	Mania	0.45	4.45	0.000	0.305
	Depression	0.24	2.31	0.024	0.052
	ADHD	0.19	2.04	0.045	0.036

CBCL = Child Behavior Checklist; VCFS = velocardiofacial syndrome; YMRS = Young Mania Rating Scale–Parent Version; ADHD = Attention-deficit/hyperactivity disorder; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version.

problems, accounting for 32%, 22%, 14%, and 8% of the variance, respectively. Complete regression results can be seen in Tables 2 and 3.

Because age was a significant predictor of depression in our group of youth with VCFS, we conducted a follow-up logistic regression analysis in which presence or absence of depression (based on the K-SADS-PL) was entered as the outcome variable, and Study Group, Age, and Study Group × Age were entered as the predictors. The overall significance of the model was calculated with the Wald statistic, which was significant (52.5; $p < 0.000$).

The Study Group × Age interaction variable was the only significant predictor (Wald statistic, 4.9; $p = 0.027$), indicating that older children with VCFS, but not older controls, had a higher incidence of depression.

DISCUSSION

In this sizeable sample of youth with VCFS, we found that relative to controls, VCFS participants were rated as having significantly elevated scores on the CBCL subscales of

TABLE 3. SIGNIFICANT PREDICTORS OF CBCL SUBSCALES IN CONTROL SAMPLE FROM SCORES ON YMRS AND DIMENSIONAL SCORES OF DEPRESSION AND ADHD FROM K-SADS-PL

Subscales	Age/symptom predictors	Beta	T score	P value	R^2 change
Anxiety	Mania	0.38	2.51	0.017	0.206
	ADHD	0.35	2.27	0.03	0.114
Depression	Depression	0.42	2.65	0.012	0.180
Somatization	Depression	0.42	2.78	0.009	0.242
	Mania	0.32	2.09	0.045	0.094
Social Problems	Mania	0.36	2.17	0.038	0.112
Thought Problems	FSIQ	−0.35	−3.50	0.002	0.320
	ADHD	0.39	4.17	0.000	0.216
	Depression	0.34	3.54	0.001	0.140
	Mania	0.32	3.12	0.004	0.081
Attention	ADHD	0.58	4.01	0.000	0.335
Rule Breaking	Mania	0.45	2.85	0.007	0.203
Aggression	Mania	0.47	3.45	0.002	0.316

CBCL = Child Behavior Checklist; YMRS = Young Mania Rating Scale–Parent Version; ADHD = attention-deficit/hyperactivity disorder; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version.

somatization, social problems, and thought problems. Despite the anecdotal reports of increased risk for manic symptoms in children with VCFS, our data suggest that manic symptoms (as measured by both the YMRS-P and the CBCL-PBD profile) do not appear to be more prevalent in VCFS than in a community sample of children with learning disorders and ADHD. Moreover, with the exception of thought problems and anxiety, manic symptoms appear to account for comparable portions of the variance in behavioral problems across both VCFS and control samples. However, in VCFS, the presence of manic symptoms is the only predictor of scores on four CBCL subscales. The presence of manic symptoms alone results in increased levels of anxiety, somatization, thought problems, and conduct problems. In contrast, the presence of manic symptoms in controls only predicts uniquely to conduct problems (rule breaking). In addition, it is noteworthy that manic symptoms in VCFS predict specifically to scores on two of the three subscales (somatization and thought problems) that are elevated relative to controls.

This suggests that, in controls, depression and ADHD symptoms must be present in conjunction with manic symptoms to be predictive of behavioral disturbance. This raises the question of whether manic symptoms can be reliably distinguished from ADHD symptoms in individuals with nonsyndromic learning disabilities. Co-morbidity between ADHD and bipolar disorder has been noted frequently (Wozniak 2005) in nonlearning–disabled samples. Although there is some overlap between the diagnostic criterion sets for ADHD and mania (e.g., distractibility), most of the diagnostic criteria do not overlap and some research shows that the overlapping criteria typically do not confound the diagnostic process (Milberger et al. 1995). Clinicians must, however, be careful not to confuse symptoms of behavioral dysregulation or low tolerance for frustration for manic symptoms; this can be avoided by careful adherence to DSM-IV criteria. Few studies have directly compared the neuropsychological profile of youth with bipolar disorder to those with ADHD (Doyle et al. 2005). However, because executive dysfunction is common to both groups (Dickstein et al. 2004; Doyle et al. 2005; Seidman 2006), and is also present in many children with learning disabilities (Gioia et al. 2002), the task of distinguishing between manic symptoms and ADHD symptoms may be particularly challenging in children with learning disabilities.

In contrast to controls, the presence of manic symptoms in children with VCFS places children with this disorder at risk for behavioral disturbance over and above the presence of either depression symptoms or ADHD symptoms. This appears to be independent of the positive relationship between depressive symptoms and age in youth with VCFS. Moreover, the presence of manic symptoms in children with VCFS is predictive of both internalizing and externalizing disorders, suggesting that manic symptoms result in greater overall behavioral dysregulation. In contrast, ADHD symptoms do not predict to this degree of behavioral dysregulation, suggesting that in VCFS, manic symptoms may constitute a phenotype that is distinct from, and potentially more severe than, an ADHD phenotype. Because pervasive behavioral dysregulation during childhood is associated with later psychopathology (Verhulste and Van der Ende 1995; Biederman et al. 2001), our findings suggest that the presence of manic symptoms in children with VCFS may increase their vulnerability to continued psychiatric problems to a greater extent than the presence of either depression or ADHD symptoms.

VCFS is associated with intellectual delays; epidemiological research suggests that psychiatric disorders are four to five times higher in children with mental retardation compared to typically developing children (Rutter et al. 1976; Koller et al. 1983). Nonetheless, these data do not explain our interesting finding that older children with VCFS, but not older controls, had a higher incidence of depression. The age association in VCFS may be related to poor psychosocial adjustment and peer difficulties; as children get older, they become increasingly dependent on the peer group and broader social milieu for learning about themselves and the world around them (Berndt 1996). Given that social difficulties are nearly

ubiquitous in VCFS (Swillen et al. 1999; Prinzie et al. 2002), it is possible that increasing social difficulties during adolescence heighten the risk for depressive symptoms. Future prospective research should address the extent to which social difficulties presage the onset of depressive symptoms in youth with VCFS.

These findings may have important clinical implications for the treatment of children with VCFS. Early assessment, diagnosis, and treatment of manic symptoms is critical to children with this disorder. It is essential that clinicians consider and integrate the behavioral and the neuropsychological correlates of manic symptoms while formulating appropriate intervention strategies. Early identification of manic symptoms in children with VCFS, and provision of appropriate interventions, may help to mitigate the relatively severe emotional and behavioral dysregulation that appears to accompany manic symptoms in children with this disorder. Hence, future psychosocial development may be enhanced and further psychiatric deterioration potentially minimized.

Our interpretation of these data is tempered, however, by the finding that, although manic symptoms are unique predictors of several CBCL subscales in children with VCFS, the overall predictive power of the model is not as strong for children with VCFS as for controls. For example, although the presence of manic symptoms is uniquely associated with thought problems on the CBCL in children with VCFS, it accounts for only 23% of the overall variance in thought problem scores. In contrast, in controls, the combination of FSIQ and symptoms of depression, ADHD, and mania account for 76% of the overall variance in thought problem scores. Similarly, whereas mania is the unique predictor of anxiety scores in children with VCFS, accounting for 10% of the total variance, the combination of symptoms of mania and ADHD in controls accounts for 32% of the overall variance in anxiety scores. This pattern is similar for somatization scores as well. This suggests that, although manic symptoms increase vulnerability to anxiety, somatization and thought problems in children with VCFS to a greater extent than symptoms of depression or ADHD, manic symptoms still account for a smaller portion of the variance than would be expected based on our control sample. Moreover, our data suggest that age and FSIQ are not contributing significantly to variance in CBCL scores in children with VCFS. This raises the important question of what is accounting for the relatively severe behavioral phenotype (characterized by increased levels of somatization, social problems, and thought problems) that children with VCFS exhibit relative to controls. Several recent reports suggest that allelic variation in the *COMT* gene, one copy of which is deleted in VCFS, may be accounting for the behavioral/psychiatric phenotype in VCFS (Bearden et al. 2004; Bearden et al. 2005; Gothelf et al. 2005). However, these findings are inconsistent, and therefore additional studies of genetic and environmental predictors are warranted.

Despite this potential caveat, the children in the current sample will be returning for follow-up in 3 years. At that time, we will be able to determine whether the natural course of manic symptoms in children with this disorder differs from controls. We will also investigate whether the cluster of manic symptoms, behavioral dysregulation, and executive dysfunction that a subset of our sample currently displays are associated with the onset of more severe psychiatric disorder, and, if so, what the nature of that disorder is. Regardless of the nature of eventual risk, however, our findings of the presence of relatively severe behavioral impairment in youth with VCFS and manic symptoms suggests that this subset of children warrants careful monitoring and treatment.

DISCLOSURES

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