

Anxiety in Boys with Attention-Deficit/Hyperactivity Disorder with and without Chronic Multiple Tic Disorder

Jayne Schneider, Ph.D., Kenneth D. Gadow, Ph.D., Judith A. Crowell, M.D., and Joyce Sprafkin, Ph.D.

Abstract

Objective: This study examined the psychosocial and behavioral concomitants of anxiety in clinic-referred boys with attention-deficit/hyperactivity disorder (ADHD) with and without chronic multiple tic disorder (CMTD).

Method: ADHD boys with ($n = 65$) and without ($n = 94$) CMTD were evaluated with measures of psychiatric symptoms, mental health risk factors, and academic and social performance.

Results: Boys with CMTD evidenced more severe anxiety and less social competence and were more likely to be living with only one biological parent than the ADHD Only group, but the magnitude of group differences was generally small. The severity of generalized anxiety, separation anxiety, social phobia, and obsessive-compulsive symptoms were uniquely associated with a different pattern of risk factors, and there was some evidence that these patterns differed for the two groups of boys.

Conclusion: Boys with CMTD had a relatively more severe and complex pattern of anxiety that was associated with different clinical features, all of which suggests that ADHD plus CMTD might better be conceptualized as a distinct clinical entity from ADHD Only. However, findings from the extant literature are mixed, and therefore this remains a topic for further study.

Introduction

THE CO-OCCURRENCE OF CHRONIC MULTIPLE TIC DISORDER (CMTD), attention-deficit hyperactivity disorder (ADHD), and anxiety disorders in children is well documented in studies with diverse methodologies including community-based and clinically-referred samples, multiple assessment strategies (e.g., rating scale, structured interview, direct observation), and in all age groups (e.g., Comings and Comings 1987a,b; Shapiro et al. 1988; Comings 1995a,b; Nolan et al. 1996; Pierre, et al. 1999; Spencer et al. 1998; Gadow et al. 2002; Sukhodolsky et al. 2003). This is likely explained by commonalities in their pathogenesis (Pauls 1992; Comings et al. 1996; Coffey et al. 2000; Alexander and Peterson 2004; Gilbert et al. 2004; Levy 2004; Stewart et al. 2006), which is nevertheless poorly understood. Studies including comparisons of children with ADHD with and without CMTD have generally found the former to be more “complex” in terms of more severe co-occurring symptomatology, greater social and academic impairment, and higher rates of pharmacotherapy (e.g., Spencer et al. 1998; Pierre et al. 1999; Gadow et al. 2002a; Freeman and Tourette Syndrome International Database Consortium 2007; Roessner et al. 2007; Grados et al. 2008; Hoekstra et al. 2008b), particularly individuals with more severe tics (e.g., Nolan et al. 1996). For example, Pierre et al. (1999) found that boys with ADHD + CMTD exhibited

more severe anxiety and mood symptoms and aggressive behaviors than peers with ADHD/–CMTD. Moreover, boys with mild tic disorder were more similar to ADHD/–CMTD peers than to patients with more severe tic disorder.

Since these early reports, others have found associations between tic severity and co-occurring psychiatric symptomatology (e.g., Mathews et al. 2007; Freeman et al. 2008; Grados et al. 2008; Mol et al. 2008) or tic complexity and impairment (e.g., Himle et al. 2007), even in cases without co-morbid ADHD (e.g., Zhu et al. 2006). Nevertheless, there have been reports of negative findings for tic severity as well (e.g., Hoekstra et al. 2004b; Khalifa and von Knorring, 2006). More recently, evidence of associations of tic severity with biologic variables suggests pathogenic heterogeneity (e.g., Bloch et al. 2006; Mathews et al. 2007; Tarnock et al. 2007; Bayam et al. 2008; Corbett et al. 2008; Gadow et al. 2008a,c; Grados et al. 2008; Lichter 2008; Orth et al. 2008; Gadow et al. 2009). In other words, individuals with more versus less severe tics may be “qualitatively” different.

Anxiety disorders (categorical model) and anxiety symptom severity (dimensional model) are commonly associated with both ADHD and tic disorder (categorical model) and tic severity (dimensional model), although the nature of these relations is poorly understood. The results of several studies indicate that anxiety is more prevalent or severe in ADHD + Tics than ADHD/–Tics

Department of Psychiatry and Behavioral Science, Stony Brook University, Stony Brook, New York.

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(e.g., Comings and Comings 1987a,b; Pierre et al. 1999; Spencer et al. 1998; Gadow et al. 2002; Roessner et al. 2007), although there are negative findings (e.g., Sukhodolsky et al. 2003; Rizzo et al. 2007). This is likely explained, at least in part, by the extraordinary diversity of methods for characterizing clinical phenotypes and assessing symptoms and procedures for identifying and recruiting cases (replication drift) and the relatively small number of subjects in diagnostic subgroups, thus limiting the ability to detect group differences.

In our own program of research, we have followed our initial studies of clinic-referred samples (Nolan et al. 1996; Pierre et al. 1999) with a large community-based survey of elementary school children (Gadow et al. 2002a). For this study, teachers completed a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV)-referenced rating scale (American Psychiatric Association 1994) for 1520 elementary school children who were later separated into one of four groups on the basis of ratings of ADHD and motor and vocal tics: ADHD Only ($n=177$), Tics Only ($n=50$), ADHD + Tics ($n=65$), and None ($n=1228$). Children with ADHD + Tics or Tics Only had more severe specific phobia and obsessive-compulsive symptoms (OCD) than pupils in the ADHD Only group. The ADHD + Tics group obtained more severe ratings of generalized anxiety disorder (GAD) and social phobia than the other three groups of children, whereas children in the Tics Only group had the most severe symptoms of social phobia (Tics Only > ADHD + Tics, ADHD Only > None). Earlier studies of referred samples have also supported an association between anxiety and tic disorder. For example, Comings and Comings (1987a) found that their Tourette's syndrome (TS) Only group evidenced higher rates of specific phobia and social phobia than ADHD with or without TS. Spencer et al. (1998) reported higher rates of specific phobia in their ADHD + TS versus ADHD Only group, but their TS Only group was not different from the other groups. Given conflicting reports and the limited information that can be gleaned from differences in prevalence rates or symptom severity, we decided that a more fruitful strategy was to see if anxiety in children with ADHD + CMTD was qualitatively different from children with ADHD Only.

Nosological research into the validity of neurobehavioral syndromes is generally modeled on the work of Robins and Guze (Robins and Guze 1970; Feighner et al. 1972), who identified several criteria for differentiating psychiatric syndromes, one of which was clinical features. In this regard they note that "the clinical picture . . . does not include only symptoms" (Robins and Guze, 1970, p. 983). The present study builds on prior findings and proposes that if ADHD with tics and ADHD without tics are indeed distinct diagnostic entities (as evidenced by differences in severity of co-occurring symptoms), it is likely that clinical features of the co-occurring symptoms also differ in clinically important ways. Although prior research has demonstrated that children with ADHD + CMTD have more severe forms of some (but not all) types of anxiety, it is unclear if this is simply the function of the fact they have more disorders or whether they have a qualitatively different type of anxiety that is perhaps linked to the CMTD diathesis.

Specifically, in this report we examine the relation of co-occurring anxiety symptoms to other coexisting psychiatric symptoms, academic and social functioning, and environmental risk/protective factors in children with ADHD/ \pm CMTD. Owing to the fact that little research has addressed the clinical features of concomitant symptoms as validators of diagnostic constructs, the present study by necessity is best characterized as exploratory (i.e.,

hypothesis generating and not hypothesis confirming). Nevertheless, differences in correlates of anxiety in the two groups of boys would support (but not confirm) the notion that ADHD + CMTD is a clinically unique syndrome. Moreover, it is our contention that better-characterized syndromes will ultimately benefit a better understanding for clinical management. Because numerous studies have reported source differences in the perceived frequency and severity of anxiety symptoms (e.g., Achenbach et al. 1987), we compare relations between variables with regard to parent and teacher ratings of anxiety separately.

Method

Participants

Two groups of boys between 6 and 12 years old who met *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, Revised (DSM-III-R) (American Psychiatric Association 1987) or DSM-IV (American Psychiatric Association 1994) diagnostic criteria for ADHD participated in this study. The groups differed with respect to the presence ($n=65$, CMTD) or absence ($n=94$, ADHD Only) of CMTD. Both groups of boys were recruited for participation in a diagnostic and follow-up study of ADHD, but only the CMTD boys participated in a double-blind, placebo-controlled clinical trial of immediate-release methylphenidate (MPH) (Pierre et al. 1999; Gadow et al. 2007; Gadow et al. 2008b). The procedure for diagnosing ADHD included structured psychiatric interviews and a battery of parent- and teacher-completed behavior rating scales (see Measures, below). To be eligible for participation, each child had to exceed the cutoff on both a parent and a teacher measure of ADHD. Specifically, the measures included the Child Symptom Inventory (Gadow and Sprafkin 2002), IOWA Conners' Teacher's Rating Scale (Loney and Milich 1982), and Mothers' Objective Method for Subgrouping (MOMS) checklist (Loney 1984). The means and standard deviations (SDs) for these measures are presented in Table 1.

Most of the boys were recruited from our child psychiatry outpatient service and a local parent support group. Additional, but secondary, sources for participant solicitation were notices to school psychologists, newspaper advertisements, and referrals from other clinicians. The latter were most relevant for the CMTD group, given the relatively low prevalence of CMTDs in the general population. The boys' mothers signed a written statement consenting to participate in the study, and the boys gave verbal assent to one of the investigators. Both the child participant and the mother were reimbursed for participation, and the study was approved by a university institutional review board.

Exclusion criteria. Children who exhibited one or more of the following were excluded from the study if: (1) their tics were the major clinical management concern; (2) they were severely ill (dangerous to self or others), psychotic, or mentally retarded (intelligence quotient [IQ] <70); or (3) had a seizure disorder, major organic brain dysfunction, major medical illness, medical or other contraindication to medication (other than tics), or pervasive developmental disorder. Children were not excluded if prior treatment with stimulants had purportedly induced or exacerbated their tics.

CMTD. The boys in the CMTD group were referred primarily for the clinical evaluation of ADHD behaviors, i.e., not tics. They all met research diagnostic criteria (Kurlan 1989) for either chronic multiple motor tic disorder ($n=3$) or Tourette's disorder ($n=62$), as determined by a comprehensive battery of physician, parent, and

TABLE 1. PARTICIPANT CHARACTERISTICS AND ADHD SYMPTOMS AT DIAGNOSIS

Characteristic	ADHD + CMTD			ADHD/-CMTD			t	p	ES(η^2)
	n	Mean	SD	n	Mean	SD			
Age	65	8.8	1.93	94	7.9	1.51	3.01	0.003	0.06
Ethnicity (nonwhite) (F/%) ^a	65	12%		94	12%		0.01	0.91	NA
IQ	45	102.0	13.50	69	103.0	12.90	0.76	0.76	
Single parent (F/%) ^a	62	21%		94	15%		0.96	0.33	NA
SES	65	34.7	9.56	94	38.6	10.71	2.41	0.02	0.04
Family income	63	3.4	.92	94	3.6	1.21	1.54	0.13	
Not married (F/%) ^a	65	63%		94	45%		5.21	0.02	NA
Medication									
Medication ever (F/%) ^a	65	45%		93	12%		21.8	0.001	
Years stimulant medication	65	0.8	1.37	93	0.1	0.45	4.04	0.001	0.12
Parent-rated ADHD									
CSI-4 ADHD-I Index	63	20.5	5.32	94	19.6	5.44	1.00	0.32	
CSI-4 ADHD-HI Index	63	16.2	6.38	94	14.7	7.19	1.32	0.19	
MOMS Hyperactivity	62	3.8	1.24	90	3.4	1.06	2.14	0.03	0.03
Teacher-rated ADHD									
CSI-4 ADHD-I Index	62	20.7	5.42	91	19.7	5.57	1.09	0.28	
CSI-4 ADHD-HI Index	62	14.1	7.75	91	14.5	7.48	0.32	0.75	
IOWA I-O subscale	62	10.8	2.87	89	10.4	3.26	0.64	0.52	
Simulated classroom									
On Task	61	79.2	20.58	83	75.3	24.36	1.04	0.30	
Fidgets	61	22.5	17.28	83	22.2	19.74	.09	0.93	
CPT									
Inattention	59	7.7	7.45	85	9.6	7.84	1.45	0.15	
Impulsivity	59	3.8	5.68	85	6.7	7.31	2.74	0.007	0.05
Dyscontrol	59	6.8	14.28	85	10.1	13.38	1.40	0.16	
Parent-rated anxiety									
Global	65	12.0	8.33	94	9.4	5.93	2.15	0.03	0.03
Generalized anxiety	63	8.3	4.67	93	6.8	4.05	2.10	0.04	0.03
Separation anxiety	62	3.4	5.05	93	2.3	2.94	1.52	0.13	
OCD	31	1.1	1.65	55	0.3	0.64	2.60	0.01	0.11
Social phobia	24	0.9	1.23	52	0.8	1.58	0.24	0.81	
Specific phobia	31	0.7	0.91	55	0.5	0.79	1.09	0.29	
Teacher-rated anxiety									
Generalized anxiety	57	7.3	4.24	91	5.7	3.45	2.41	0.02	0.04
OCD	30	0.5	1.01	51	0.3	0.66	1.19	0.24	
Social phobia	28	0.9	1.01	52	0.7	1.56	0.62	0.54	
Specific phobia	30	0.2	0.55	51	0.04	0.20	1.54	0.13	
Co-occurring symptoms									
Parent-rated ODD/CD	62	13.2	9.48	94	13.2	9.31	0.02	0.98	
Parent-rated aggression	62	2.5	1.92	90	2.1	1.83	1.34	0.18	
Parent-rated depression	63	5.4	4.70	94	3.9	3.65	2.36	0.02	0.04
Teacher-rated ODD/CD	59	9.4	9.16	91	9.9	8.69	0.31	0.76	
Teacher-rated aggression									
Teacher-rated depression	60	4.4	4.58	91	3.2	3.66	1.78	0.08	
Impairment									
CBCL Social	65	4.0	2.18	94	4.7	1.76	2.30	0.02	0.03
TRF Academic	65	2.2	0.65	94	2.4	0.63	1.50	0.14	

^aChi-squared analyses.

Abbreviations: ADHD = Attention-deficit/hyperactivity disorder; CMTD = chronic multiple tic disorder; SD = standard deviation; ES = effect size (partial eta2); NA = not available; IQ = intelligence quotient; SES = socioeconomic status; NA = not applicable; CSI-4 = Child Symptom Inventory-4; MOMS = Mothers' Objective Method for Subgrouping; CPT = Continuous Performance Test; OCD = obsessive compulsive disorder; CD = conduct disorder; CBCL = Child Behavior Checklist; TRF = Teacher's Report Form; F/% = frequency/%; ODD = oppositional defiant disorder.

teacher-completed assessment instruments and videotaped observations of child behavior in a clinic-based simulated classroom (Gadow et al. 2007). In addition, at least two reliable examiners in different settings witnessed motor tics in all patients assigned to this group. In DSM-IV nomenclature, the boys met criteria for either Tourette's disorder or chronic tic disorder. The Global Severity Score (GSS) of the Yale Global Tic Severity Scale (Leckman et al.

1989) for each child in this group, ranged from mild to severe ($M = 38.06$; $SD = 16.61$). The majority ($n = 57$) participated in a treatment study that evaluated the safety and efficacy of MPH for ADHD symptoms (Gadow et al. 2007).

ADHD Only. The boys in this group ($n = 94$) were evaluated and determined not to have a tic disorder (neither simple nor

multiple) after careful evaluation using the Child Habits and Tics Screening Checklist (Gadow 1991) and a modified version of the Diagnostic Interview for Children and Adolescents–Parent version (DICA-P) (Reich 2000), which incorporated screening questions based on the Yale Global Tic Severity Scale (YGTSS), and was confirmed by videotaped observations in a simulated classroom.

Co-morbidities. Co-morbid diagnoses were assessed with the Diagnostic Interview for Children and Adolescents (DICA) (Reich 2000), which was routinely administered to the mothers of all but the first 11 children. Of the interviewed cases ($n=146$), 50% ($n=26$) of boys with CMTD and 37% ($n=35$) of boys with ADHD Only were co-morbid for oppositional defiant disorder (ODD). Of those, 2 with CMTD and 6 with ADHD Only also met criteria for conduct disorder (CD). A number of children (15 CMTD; 21 ADHD Only) received scores for either overanxious or GAD and/or had simple phobia. The majority of children with major depressive or dysthymic disorder diagnoses (9 CMTD; 4 ADHD Only) also had an anxiety disorder. One boy in the CMTD group met DICA diagnostic criteria for OCD, i.e., his compulsions were determined not to be better characterized as complex motor tics.

Measures

Demographic variables. The Parent Questionnaire (Gadow et al. 2008a) included questions pertaining to marital status, family income, and parental education and employment from Hollingshead's (1975) criteria. Additional questions pertained to the child's age, gender, ethnicity, and educational and medical history, including treatment with psychotropic medication.

Psychiatric symptom ratings. Mothers and teachers rated child symptoms using the Child Symptom Inventory-4 (CSI-4) (Gadow and Sprafkin 2002), which contains the behavioral symptoms of most childhood disorders described in the DSM-IV. Individual items bear a one-to-one correspondence with DSM-IV symptoms. Symptom severity is assessed as follows: 0 = never, 1 = sometimes, 2 = often, 3 = very often. In this study, we used severity scores for parent rated ADHD:Inattentive (ADHD:I, 9 items), ADHD:Hyper-Impulsive (ADHD:HI, 9 items), GAD, and separation anxiety disorder (SAD) (8 items each, parents only). For a subsample of boys, revision of the CSI-4 allowed us to also obtain ratings of obsessive-compulsive (2 items), social phobia (3 items), and specific phobia (1 item) symptoms; number of mother/teacher ratings was as follows: ADHD Only ($n=55/51$) and CMTD ($n=31/30$). Teacher-rated severity scores were based on the same number of items for each category with the exception of GAD (7 items). Using the same CSI-4 severity scores, we also created three summary scores: Parent ratings of global anxiety (GAD, SAD, one social phobia item), aggression (ODD and CD symptoms) rating, and depression rating (major depressive and dysthymia symptoms). Numerous studies indicate that the CSI-4 demonstrates satisfactory internal consistency (Cronbach α), reliability, and convergent and discriminant validity in community-based normative, clinic-referred, and ADHD samples (Gadow and Sprafkin 2007). CSI-4 scores are minimally correlated with age, IQ, or socioeconomic status (SES).

In addition, teachers also completed the IOWA Conners' Teacher's Rating Scale (Loney and Milich 1982), which contains two 5-item subscales: Inattention–Overactivity (I-O) and Oppositional–Defiant (O-D), whereas mothers completed the MOMS, which contains 10 symptoms arranged in a checklist format and gener-

ates a Hyperactivity scale score and an Aggression scale score (Loney 1984). Both informants completed the Peer Conflict Scale (Nolan and Gadow 1994), which contains 10 items and is used with parents and teachers to assess aggressive interactions with other children.

Tic ratings. The diagnosing physician evaluated each child's tic disorder using the YGTSS, from which the GSS was used in this study. The clinician was instructed to complete all tic scales for tics but not for associated co-morbidities (Gadow et al. 2002a). The strong relation between tic severity and tic impairment is evident in the large correlation ($r=0.83$, $p<0.001$) between YGTSS Total Tic Severity Score and Global Tic Severity scores for the CMTD boys. Parents and teachers indicated their perception of tic severity using the Global Tic Severity Scale (GTRS) (Nolan et al. 1994).

Laboratory ADHD tasks. There were two laboratory ADHD measures, the simulated classroom and the Continuous Performance Test (CPT). For the simulated classroom (Roberts et al. 1984), the child sat alone at a desk in a small classroom and was instructed to complete worksheets and not to play with toys on an adjacent table. The 15-minute, videotaped observation session was divided into 180 5-second intervals, and behaviors were coded as either present or not present in each interval. The behaviors coded by observers during these periods are those traditionally associated with ADHD and include attention to task (On Task) and motor activity (Fidgetiness). For the CPT (Halperin et al. 1992), the child was instructed to press the space bar whenever the letter "A" follows the letter "X" on the screen. The entire task lasts about 12 minutes, and three scores: Inattention, impulsivity, and dyscontrol.

Academic and social functioning. The mean score of the Academic Functioning subscale of the Teacher Report Form (TRF) of the Child Behavior Checklist (CBCL) (Achenbach 1991b) was used as a measure of the teacher's perception of academic performance. For this subscale, the child's level of academic performance is rated on a scale from 1 (far below) to 5 (far above grade level). The mean score for the Social Competence subscale of the CBCL (Achenbach 1991a) was used as a measure of social functioning, and is rated on a scale from 0 to 12. The parent rates their child's participation in organizations, number of friends, frequency of contact, behavior with peers, and behavior alone.

Procedure

Following a telephone screening interview, parents wishing to participate in the study were mailed a packet of rating scales. Parents also received a school assessment package that contained an explanatory letter, a parental release of information form, a self-addressed envelope, and teacher questionnaires. It was the parents' responsibility to take the assessment package to the teacher, who mailed it to the project director when completed. Upon receipt of parent and teacher ratings, mother and child were scheduled for a clinic evaluation. Child assessments included two laboratory-based measures of ADHD symptoms, the Simulated Classroom, and the CPT. The former was also used to document tic frequency. The DICA-P was administered to the mother of each boy by a researcher, trained by the instrument's developer, with practice sessions to achieve acceptable reliability. With the exception of 13 boys in the CMTD group, parents were interviewed using an abridged version of the DICA-P, which included the behavioral symptoms for the disruptive behavior disorders and anxiety and mood disorders.

Statistical analyses

Chi-square and *t*-tests for categorical and continuous variables, respectively, were used to examine differences between samples in demographic characteristics, ADHD symptom severity, co-occurring psychiatric symptoms, impairment, and risk/protective factors (Table 1). To gauge the magnitude of group differences, effect size (percentage of variance in dependent variables accounted for by presence or absence of CMTD) for independent groups was calculated using partial eta-squared (η^2). As a general rule of thumb for determining the magnitude of correlations, Cohen (1988) suggests the following: $\eta^2 > 0.25$ = large, 0.25–0.09 = moderate, and 0.09–0.01 = small. We report significant group differences ($p < 0.05$) with an $\eta^2 \geq 0.03$, which corresponds to a correlation of 0.17 or larger.

To examine the unique as well as combined ability of child and family characteristics to predict anxiety, we examined the symptom ratings of the parent and teacher versions of the CSI-4 for different forms of anxiety. Symptom ratings were summed as follows: All anxiety symptoms for parents and teachers were summed separately to obtain a parent-rated and a teacher rated Global Anxiety score. Individual dimensions of anxiety symptoms were also summed to yield scores for GAD, SAD, OCD, and social phobia. (For ease of presentation, the anxiety dimensions are referred to by their diagnostic labels, but it should be noted that they refer to dimensions of anxiety and not true categories.)

Using regression analyses to predict anxiety dimensions, we simultaneously entered all predictors (risk factors) significantly correlated with each dimension of anxiety ($p \leq 0.10$) separately to predict the parent- and teacher-rated anxiety dimensions controlling for statistically significant demographic variables where indicated. We did this knowing that some of the predictors would be included in the regression analyses just by chance, and that those not contributing significantly to the variance would be screened out in this second stage. Our intent was to be over inclusive at first, so as to avoid the possibility of missing factors that might turn out to be unique predictors. For these analyses, the predictors were as follows: SES, not living with biological parent, single-parent home, family income, social functioning (CBCL), academic functioning (TRF), and parent and teacher CSI-4 ratings (ADHD:I, ADHD:HI, aggression, depression). In addition, for the CMTD group, we included the parent and teacher GTRS Total score and YGTSS GSS score. Of particular interest were variables that accounted for a portion of the variance in anxiety over and above other correlated variables (unique predictors).

Given the unreliability of interaction tests with samples of this size, the following exploratory analyses were performed primarily as a means for generating hypotheses for future study. We were particularly interested in the possibility of interaction effects, which would suggest that different risk factors are associated with phenotypically similar co-occurring anxiety symptoms for each group. Analysis of variance (ANOVA) testing for significant differences between *r* values was conducted for all risk factors that, based on Pearson correlations, appeared to be significantly related to a particular type of anxiety in one group versus the other.

Results

Group differences

Demographic characteristics. The two groups differed with respect to age (CMTD > ADHD Only; $\eta^2 = 0.06$), SES (ADHD Only > CMTD; $\eta^2 = 0.04$), divorce/separation of biological par-

ents (CMTD > ADHD Only; 63% vs. 45%), ever received psychotropic medication (CMTD > ADHD Only; 45% vs. 12%), and years of previous stimulant medication (CMTD > ADHD Only; $\eta^2 = 0.12$), but not with respect to family income, ethnicity, or single parent status (Table 1). Although IQ scores were not available for all children, there was no significant group difference in IQ for those children (72%) whose scores we obtained.

Do the boys have similar ADHD clinical phenotypes?

The first step in our analyses was to determine if the two groups of boys have similar ADHD clinical phenotypes. The two groups of ADHD boys were compared on a variety of ADHD measures to determine their similarity with regard to the frequency and severity of ADHD symptoms (Table 1). The two groups were highly similar in ADHD clinical phenotypes and differed only with regard to MOMS Hyperactivity ($\eta^2 = 0.03$; ADHD Only > CMTD) and CPT impulsivity ($\eta^2 = 0.05$; CMTD > ADHD Only). These differences were small.

Is the CMTD group more impaired?

Boys with CMTD were reported to have more impaired social functioning (CBCL) than the ADHD Only group ($p = 0.023$), but the magnitude of this difference was small ($\eta^2 = 0.03$). The two groups did not differ in terms of academic functioning as reported by teachers (TRF).

Do the boys have similar aggression clinical phenotypes?

The two ADHD groups did not differ in the severity of aggression (Table 1). Therefore, not only were the boys highly similar in the severity of their ADHD, they were also similar in terms of the most common “co-morbidity” associated with ADHD.

Do the two groups of boys differ in severity of anxiety symptoms?

The groups differed (CMTD > ADHD Only) for mothers' ratings of global anxiety ($p = 0.034$; $\eta^2 = 0.03$), GAD ($p = 0.037$; $\eta^2 = 0.03$), and OCD ($p = 0.014$, $\eta^2 = 0.11$) (Table 1). Teacher's ratings (CSI-4T) indicated groups differences (CMTD > ADHD Only) for GAD ($p = 0.017$, $\eta^2 = 0.04$).

Do the two groups of boys differ in severity of depression symptoms?

The two ADHD groups also differed (CMTD > ADHD Only) in the number of co-occurring symptoms of depression ($p = 0.02$; $\eta^2 = 0.04$), as reported by their mothers.

Do mothers and teachers agree about the severity of anxiety?

Correlations between mothers' and teachers' ratings of anxiety symptoms within each group of boys were low and not significant with the exception of social phobia: CMTD ($r = 0.46$) and ADHD Only ($r = 0.59$).

What study variables are associated with global anxiety?

Mothers' ratings of ADHD Only boys. Thirteen study variables were significantly correlated with the severity of at least one

mother-rated CSI-4 anxiety variable in the ADHD Only group (see Table 2). Nine variables were correlated with Global Anxiety scores accounting for 47% of the variance in global anxiety. Regression analyses indicated mother-rated social functioning and depression uniquely predicted global anxiety.

Mothers' ratings of CMTD boys. Fourteen of the study variables were significantly correlated with the severity of at least one type of mother-rated child anxiety in the CMTD group (Table 3). Ten variables were correlated with Global Anxiety scores accounting for 63% of the variance in global anxiety. Regression analyses indicated that mothers' depression ratings were uniquely predictive of global anxiety.

What study variables are associated with specific types of anxiety?

Mothers' ratings of ADHD Only boys. Explained variance with study variables was as follows: GAD (57%), SAD (22%), OCD (not significant [NS]), and social phobia (35%) (Table 2). Mothers' ratings of inattention and depression were unique predictors of mother-rated GAD; single-parent household was a unique predictor of mother-rated SAD; and social (CBCL) and academic (TRF) performance were unique predictors of mother-rated social phobia.

Mothers' ratings of CMTD boys. Explained variance was as follows: GAD (73%), SAD (36%), OCD (22%), and social phobia (NS) (Table 3). Mothers' ratings of depression were uniquely predictive of mother-rated GAD. Teacher's ratings of hyperactivity-impulsivity uniquely predicted mother-rated GAD scores (i.e., cross-informant prediction). Mothers' inattention ratings were uniquely predictive of mother-rated SAD.

Teachers' ratings of ADHD Only boys. With regard to specific types of anxiety, explained variance with study variables was as follows: GAD (58%), OCD (31%), and social phobia (NS) (Table 2). Teachers' ratings of hyperactivity-impulsivity and depression were uniquely predictive of teacher-rated GAD, and teachers' ratings of depression also predicted teacher-rated OCD.

Teachers' ratings of CMTD boys. Explained variance with study variables was as follows: GAD (64%), OCD (NS), and social phobia (28%) (Table 3). Teachers' ratings of depression were unique predictors of GAD and social phobia. Teachers' ratings of hyperactivity-impulsivity were also uniquely predictive of teacher-rated GAD.

Is anxiety "different" in ADHD boys with versus without CMTD?

Mothers' ratings of anxiety. Exploratory Group×Variable interaction analyses revealed that the (1) association between mothers' ratings of inattention and SAD and (2) cross-informant association between teachers' ratings of hyperactivity-impulsivity and mothers' ratings of global anxiety and GAD were significantly stronger for children with CMTD than for those with ADHD Only, both of which were also significant with a Bonferroni correction, $p < 0.0025$ (Table 4). These findings provide preliminary evidence for our hypothesis that different processes may operate for the two groups of boys with respect to the role of risk factors and anxiety. In addition, owing to reduced sample size, we also note that the interaction of three risk factors (social functioning, teacher-rated ADHD:I, and ADHD:HI) and mothers' ratings of social phobia approached significance.

TABLE 2. SIGNIFICANT BIVARIATE CORRELATIONS (r) AND STANDARDIZED REGRESSION COEFFICIENTS (β) FOR RATINGS OF CHILDREN WITH ADHD-CMTD ($N=94$): RISK FACTORS AT INTAKE PREDICTING ANXIETY AT INTAKE

Risk/protective factor	Parent-rated CSI-4 anxiety								Teacher-rated CSI-4 anxiety							
	Global		GAD		SAD		OCD ^a		Social phobia ^a		GAD		OCD ^a		Social phobia ^a	
	r	β	r	β	r	β	r	β	r	β	r	β	r	β	r	β
SES	-0.08		-0.14		0.04		0.06		-0.12		-0.12		-0.26	-0.14	-0.02	
Not with biological parent	0.19	-0.04	0.15		0.18	-0.18	0.07		0.05		0.14		-0.05		-0.16	
Single-parent home	0.17	0.12	0.05		0.27	0.41	0.08		0.09		0.12		-0.04		-0.14	
Family income	-0.10		-0.10		-0.08		-0.12		-0.06		-0.17		-0.11		0.06	
Social (CBCL)	-0.38	-0.20	-0.35	-0.11	-0.24	-0.18	-0.13		-0.45	-0.32	-0.06		-0.21		-0.23	-0.20
Academic (TRF)	-0.16		-0.10		-0.18	-0.19	-0.21		-0.26	-0.26	-0.10		-0.17		-0.24	-0.21
Parent CSI-4																
ADHD:I	0.32	0.06	0.41	0.20	0.08		0.22		-0.11		0.07		-0.03		0.04	
ADHD:II	0.36	0.12	0.38	0.12	0.20	0.07	0.07		0.27	0.14	0.07		0.17		-0.10	
Aggression	0.48	0.11	0.50	0.01	0.23	0.13	0.28	0.22	0.04		0.09		0.01		-0.08	
Depression	0.61	0.46	0.70	0.62	0.24	0.06	0.23	0.12	0.22		0.31	0.03	0.35	0.18	0.09	
Teacher CSI-4																
ADHD:I	0.02		0.02		0.04		0.00		0.16		0.39	0.15	0.02		0.22	
ADHD:II	0.07		-0.00		0.17		-0.04		0.38	0.26	0.27	0.28	0.24	0.20	0.02	
Aggression	0.20	-0.02	0.18	-0.03	0.14		-0.02		0.07		0.30	-0.07	0.19		-0.08	
Depression	0.20	-0.02	0.21	-0.09	0.10		0.18		0.01		0.69	0.67	0.45	0.36	0.17	

Bold items: (r values) $p \leq 0.10$; (β values) $p \leq 0.05$.

^aSmaller sample sizes.

Abbreviations: ADHD = Attention-deficit/hyperactivity disorder; CMTD = chronic multiple tic disorder; CSI-4 = Child Symptom Inventory-4; GAD = generalized anxiety disorder; SAD = separation anxiety disorder; OCD = obsessive-compulsive disorder; SES = socioeconomic status; CBCL = Child Behavior Checklist; TRF = Teacher Report Form.

TABLE 3. SIGNIFICANT BIVARIATE CORRELATIONS (*r*) AND STANDARDIZED REGRESSION COEFFICIENTS (*β*) FOR RATINGS OF CHILDREN WITH ADHD + CMTD (*N* = 65): RISK FACTORS AT INTAKE PREDICTING ANXIETY AT INTAKE

Risk/protective factor	Parent-rated CSI-4 Anxiety								Teacher-rated CSI-4 Anxiety							
	Global		GAD		SAD		OCD ^a		Social phobia ^a		GAD		OCD ^a		Social phobia ^a	
	<i>r</i>	<i>β</i>	<i>r</i>	<i>β</i>	<i>r</i>	<i>β</i>	<i>r</i>	<i>β</i>	<i>r</i>	<i>β</i>	<i>r</i>	<i>β</i>	<i>r</i>	<i>β</i>	<i>r</i>	<i>β</i>
SES	-0.06		-0.10		-0.05		-0.03		-0.29		0.04		-0.25		-0.11	
Not with biological parent	0.21	0.14	0.14		0.19		0.17		0.34		-0.23	-0.02	0.05		0.06	
Single parent	-0.01		-0.08		0.05		-0.12		-0.02		-0.16		0.14		-0.08	
Family Income	-0.13		-0.02		-0.20		-0.05		-0.26		0.13		-0.13		-0.16	
Social (CBCL)	-0.24	-0.07	-0.29	-0.11	-0.13		0.19		-0.18		-0.17		-0.10		-0.16	
Academic (TRF)	-0.08		-0.07		-0.10		-0.09		0.18		-0.01		-0.05		0.00	
Parent CSI-4																
ADHD:I	0.49	0.19	0.52	0.13	0.34	0.28	0.19		0.31		-0.13		0.08		0.08	
ADHD:II	0.23	0.08	0.24	0.21	0.17		0.19		-0.02		0.05		0.05		0.01	
Aggression	0.49	0.16	0.49	0.01	0.37	0.24	0.00		0.12		-0.00		0.01		0.13	
Depression	0.69	0.35	0.80	0.62	0.40	0.01	0.30		0.31		0.12		0.01		-0.05	
Teacher CSI-4																
ADHD:I	-0.16		-0.18		-0.13		-0.18		-0.50		0.26	0.03	-0.02		0.02	
ADHD:II	-0.27	-0.21	-0.33	-0.27	-0.18		0.10		-0.28		0.30	0.29	0.03		-0.08	
Aggression	-0.09		-0.14		-0.04		-0.33	-0.33	-0.11		0.44	-0.17	-0.06		0.24	
Depression	0.18		0.13		0.17		-0.22		-0.15		0.70	0.71	0.02		0.46	0.42
Tic severity																
Parent GTRS	0.45	0.30	0.39	0.06	0.47	0.48	0.32	0.33	0.08		0.34	-0.12	0.39	0.28	0.11	
Teacher GTRS	0.26	0.00	0.28	0.09	0.18		0.21		0.22		0.41	0.33	0.36	0.20	0.34	0.27
YGTSS	0.36	-0.13	0.35	-0.15	0.27	-0.20	0.30		0.05		0.26	0.04	0.16		-0.02	

Bold items: (*r* values) $p \leq 0.10$; (*β* values) $p \leq 0.05$.

^aSmaller sample sizes.

Abbreviations: ADHD = Attention-deficit/hyperactivity disorder; CMTD = chronic multiple tic disorder; GAD = generalized anxiety disorder; SAD = separation anxiety disorder; OCD = obsessive-compulsive disorder; SES = socioeconomic status; CBCL = Child Behavior Checklist; TRF = Teacher Report Form; CSI-4 = Child Symptom Inventory-4; GTRS = Global Tic Severity Scale; YGTSS = Yale Global Tic Severity Scale.

Is tic severity associated with anxiety?

All three tic severity ratings (mothers, teachers, clinician) were correlated ($r \geq 0.20$) with at least one type of mother-rated and teacher-rated anxiety measure. Regression analyses indicated that mothers' ratings of tic severity ratings uniquely predicted mother-rated global anxiety and SAD, and teachers' ratings of tic severity uniquely predicted only teacher-rated GAD (see Table 3).

Discussion

The findings of the present study illustrate the complexity of our current nosological rules for conceptualizing neurobehavioral syndromes when applied to a fairly simple question about differences between two groups of boys with ADHD; namely, "Is symptom anxiety quantitatively and qualitatively different in boys with ADHD with and without CMTD?" The problem is even more glaring when one considers that we examined only one part (association with anxiety) of one criterion (phenomenology) for only one co-morbidity (CMTD) and only two informants and with a highly restricted range of broadly characterized "predictor" variables.

This having been said, the findings of this study suggest that to some extent the various types of anxiety symptoms were associated with a different pattern of child and home environmental characteristics, but more importantly, these relations varied for children with ADHD with and without CMTD. In other words, anxiety in the two groups of boys appears to be qualitatively different. Moreover, relations among variables also varied as function of informant

(mother vs. teacher), all of which likely have implications for a better understanding of etiology and possibly treatment and clinical management. Although we did not specifically test for differences between specific types of anxiety symptoms, variation in the pattern of obtained correlations with risk factors supports nosological distinctions (i.e., different pathogenesis) and is consistent with the findings from laboratory animal (e.g., Turri et al. 2001; Hovatta and Barlow 2008) and human (e.g., Hirshfeld et al. 2008; Hovatta and Barlow 2008; Smoller et al. 2008) studies. Our results are also in general agreement with the idea that ADHD with and without CMTD may be distinct clinical phenotypes characterized by anxiety with different clinical features (and possibly different etiology).

Global anxiety

According to parents' ratings, the CMTD group had more severe global anxiety than the ADHD boys, but the magnitude of group difference was small. Although a number of variables correlated with ratings of global anxiety in each group of boys, few were uniquely predictive. As expected, depression was a unique predictor of global anxiety for both groups of boys. However, for the ADHD Only group, mothers' ratings of social functioning were also unique predictors of global anxiety, whereas for the CMTD group, mother's ratings of tic severity were uniquely predictive. This differential pattern of associations between anxiety, ADHD, and tic severity suggest that not only is anxiety different in the two groups of boys, who were comparable in ADHD severity, but that their ADHD may be qualitatively different as well. It is also possible that the motor

TABLE 4. TESTS (ANOVAs) OF INTERACTION EFFECTS BETWEEN GROUPS (ADHD ± CMTD) FOR RISK FACTORS PREDICTING ANXIETY

Type of anxiety: risk factor	ADHD + CMTD			ADHD/–CMTD			F	p
	n	r	p	n	r	p		
Parent-rated global anxiety								
Social (CBCL)	65	–0.24	0.053	94	–0.38	0.000	0.10	0.751
Parent-rated ADHD:HI	63	0.23	0.065	94	0.36	0.000	2.35	0.127
Teacher-rated ADHD:HI	62	–0.27	0.033	91	0.07	0.492	10.81	0.001
Parent-rated GAD								
Parent-rated ADHD:HI	63	0.24	0.057	93	0.38	0.000	2.71	0.102
Teacher-rated ADHD:HI	61	–0.33	0.009	90	0.00	0.982	10.17	0.002
Teacher-rated depression	59	0.13	0.327	90	0.21	0.044	0.07	0.792
Parent-rated SAD								
Single parent	60	0.05	0.709	93	0.27	0.008	0.70	0.405
Social (CBCL)	62	–0.13	0.302	93	–0.24	0.021	0.70	0.403
Parent-rated ADHD:I	62	0.34	0.006	93	0.08	0.444	6.07	0.015
Parent-rated OCD								
Parent-rated aggression	31	0.00	0.998	55	0.28	0.039	0.49	0.488
Parent-rated social phobia								
Social (CBCL)	24	–0.18	0.408	52	–0.45	0.001	2.34	0.13
Teacher-rated ADHD:I	24	–0.50	0.013	49	0.16	0.260	2.71	0.11
Teacher-rated ADHD:HI	24	–0.28	0.187	49	0.38	0.007	2.64	0.11
Teacher-rated GAD								
Parent-rated depression	57	0.12	0.359	91	0.31	0.003	0.98	0.323
Teacher-rated ADHD:HI	57	0.26	0.051	91	0.39	0.000	0.02	0.904
Teacher-rated OCD								
Parent-rated depression	30	0.01	0.978	51	0.35	0.013	0.52	0.472
Teacher-rated depression	30	0.02	0.919	51	0.45	0.001	1.27	0.263
Teacher-rated social phobia								
Teacher-rated depression	28	0.46	0.013	52	0.17	0.237	0.52	0.474

Bold items: F value indicating significant group×risk factor interactions ($p < 0.05$).

Abbreviations: ADHD = Attention-deficit/hyperactivity disorder; CMTD = chronic multiple tic disorder; CBCL = Child Behavior Checklist; ADHD:HI = ADHD-Hyperactive-Impulsive; GAD = generalized anxiety disorder; SAD = separation anxiety disorder; OCD = obsessive-compulsive disorder.

activity associated with tics and OCD behaviors may influence ratings of ADHD behaviors in the CMTD group. Regardless, it is important to note that the two groups of boys performed similarly on objective laboratory measures of ADHD behaviors.

Exploratory interaction analyses revealed that the magnitude of the cross-informant association between teachers' ratings of hyperactivity-impulsivity and mothers' ratings of global anxiety was significantly larger for the CMTD than for the ADHD Only boys. In other words, hyperactive-impulsive behaviors in the classroom were negatively correlated with mother's ratings of global anxiety, but this was true only for the CMTD boys. Although it is difficult to interpret similarities and differences in cross-informant correlations, we note it here because the group interaction achieved significance even with a Bonferroni correction. For the CMTD group, it is possible that the boys were differentially more successful in inhibiting negativistic behaviors (ADHD, tics) so as not to draw attention to themselves by eliciting teacher reprimands and subsequent negative peer reactions. The converse may be true when these boys return home. Those who suppressed their behaviors the most in school may be more likely to act out (ADHD, tics) at home, which their mothers' attribute to anxiety owing to concomitant tic activity. We realize this is a matter of speculation, but it is a testable hypothesis. Regardless, this finding provides preliminary evidence for our assertion that different processes may operate for the two groups of boys with respect to the role of risk factors and anxiety, and warrants further examination in future studies.

Social phobia

There were no group differences in the severity of social phobia for either informant, which was the only anxiety dimension for which mother and teacher ratings were even moderately correlated. Although many study variables were associated with social phobia, few were uniquely predictive. The exceptions were social and academic performance, as rated by parents and teachers, respectively, which were unique predictors of mother's ratings of social phobia in boys with ADHD Only; however, this was not the case for the CMTD group. One possible explanation for this finding is that social phobia in boys with ADHD Only is more related to performance deficits resulting from their ADHD. Although boys with CMTD also likely experience similar performance deficits for many of the same reasons, they also must confront the embarrassment and social rejection associated with their co-occurring tics, which may play a more powerful role in their social phobia. Teachers' ratings appear to support a similar interpretation; their ratings of depression were unique predictors of social phobia, but only in boys with CMTD.

Generalized anxiety

Boys with CMTD received higher GAD severity scores from both their mothers and teachers, but the magnitude of these differences was small. In both groups of boys, we found that mothers' and teachers' ratings of depression symptoms were unique predictors of GAD severity; however, the relation between ADHD

symptoms and GAD was more variable. Teacher-rated hyperactivity–impulsivity was uniquely predictive of teacher-rated GAD in both groups of boys. However, for the ADHD Only boys, mothers' ratings of inattention were uniquely predictive of mother-rated GAD, whereas, for the CMTD group, teachers' ratings of hyperactivity–impulsivity were unique predictors (inversely related). There was additional within-informant association for the CMTD group; teacher-rated tic severity (GTRS) was a unique predictor of teacher-rated GAD severity. Exploratory interaction analyses resulted in essentially the same findings as reported for parent-rated global anxiety regarding group differences in relations between variables.

Separation anxiety

Although groups did not differ in severity of SAD symptoms, the single-parent household was uniquely associated with SAD, but just for the ADHD Only boys. This is consistent with findings in other studies of an association between child separation anxiety and divorce (Kasen et al. 1996; Chorpita and Barlow 1998; Pagani et al. 2006), and suggests that boys with ADHD Only react similarly to children from the general population to this stressor. In contrast, for boys with CMTD, severity of tics (GTRS), and to lesser extent severity of inattention, were uniquely predictive of SAD. Similarly, in their pioneering study of anxiety disorders in children with TS, Coffey et al. (2000) found that the prevalence of SAD most clearly differentiated children with more severe TS (i.e., controlling for presence of other anxiety disorders). They offered two hypotheses to explain group differences: (1) Anxiety-induced sensitization of central nervous system tic mechanisms and (2) adaptive response (SAD) to social stigmatization associated with more severe tics. In the present study, a plausible explanation for the relation between inattention symptom severity and SAD is wanting.

Obsessive-compulsive symptoms

Parents (but not teachers) rated the CMTD group as having more severe OCD symptoms than the ADHD Only group. Moreover, the magnitude of this group difference was in the moderate range and clearly the largest of all the anxiety measures. This finding was not unexpected and supports a well-established association between the two disorders (e.g., Pauls et al. 1995; Peterson et al. 2001; Leckman et al. 2003; Himle et al. 2007; Roessner et al. 2007; Grados et al. 2008; Mathews et al. 2007; Mol et al. 2008), to include covariation in severity over time (Lin et al. 2002) and association with more severe TS (Coffey et al. 2000). Curiously, in the present study, with the exception of teacher-rated depression in the ADHD Only group, none of the other study variables was uniquely predictive of OCD severity in either or both group of boys, to include tic severity. However, the CMTD sample size for these analyses was small; therefore, replication with larger samples is necessary before drawing firm conclusions about OCD symptom findings.

With regard to the extant literature, there is also evidence that the two disorders are pathogenically unique (e.g., Bloch et al. 2006; Klaffke et al. 2006; Himle et al. 2007; Lin et al. 2007; Grados et al. 2008), and it is also likely that the nature of their interrelation varies across individuals (i.e., pathogenic heterogeneity within each clinical phenotype) (e.g., Leckman et al. 2003; Grados et al. 2008), which if correct increases exponentially the complexity of their associations.

Medication histories

The two groups of boys differed with regard to prior experience with psychopharmacotherapy, which is not unexpected owing to the facts that: (1) The ADHD + CMTD group had more than one

disorder for which drugs are prescribed and (2) they were enrolled in a clinical trial (i.e., many were previously diagnosed and dissatisfied with their current medication) whereas (3) the ADHD Only group was being offered a free diagnostic evaluation for participating in a follow-up study and serving as a comparison group for the ADHD + CMTD boys. In view of the fairly compelling evidence that ADHD + CMTD, particularly with more severe tics, is associated with a more troubling clinical presentation, it is not unexpected that they were more likely to be diagnosed and treated than children with ADHD Only. For example, the data from our community-based survey (Gadow et al. 2002a) of elementary school children indicated that current treatment prevalence rate for children who met symptom cutoff for ADHD was higher for the ADHD + Tics group than for the ADHD Only group.

The significance of differences in treatment histories with regard to understanding group differences in anxiety in the present study is limited owing to following: (1) Both groups were virtually identical in ADHD severity; (2) neither group was recruited for co-occurring anxiety (i.e., no referral bias); (3) none of the ADHD + CMTD boys had received medication for anxiety; (4) anxiety is not a recognized indication for MPH nor have CNS stimulants been shown to be particularly effective for the management of anxiety; and (5) there is no compelling evidence that stimulants exacerbate anxiety in either group of boys (Gadow et al. 2002b; Pliszka 2007). In other words, neither the boys' medication histories, seeking treatment in the randomized clinical trial, or the reason for participating in the study had anything to do with anxiety. In addition, one of the most common reasons for medical referral in children is co-occurring aggression, and ODD/CD is the most common "comorbidity" in children with ADHD. In the present study, both groups of boys obtained comparable ratings of ODD/CD severity from both parents and teachers.

Limitations

Interpretation of these study findings is subject to several qualifications. Cross-sectional analyses do not address the issue of causality or the direction of influence. For example, whether social and academic difficulties cause anxiety in one or both groups can only be determined with longitudinal research. In this study, we examined co-occurring anxiety from a dimensional versus categorical perspective, raising questions about the generalization of findings to diagnosed anxiety disorder. However, the general convergence in findings for both strategies (categorical and dimensional) in the extant literature strongly suggests that each is useful in generating models for clinical phenotypes. Generalizations about this study's findings are bounded by sample characteristics and methodology to include assessment instruments and therefore may not apply to females, older children, children with very mild or very severe tics, or self-reported symptoms or to different measures of anxiety, ADHD symptoms, or tics. It is important to note that our interaction analyses were limited by sample size, and negative findings may simply reflect insufficient statistical power. This also applies to our findings for specific phobia, social phobia, and OCD symptoms. The present study used a very restricted range of broadly characterized variables.

It is likely that a more molecular strategy that incorporated variables previously documented to be associated with specific types of anxiety would provide more insight into group differences. Last, we offer the following caveat: Because the current nosological system for childhood neurobehavioral syndromes is based more on clinical convenience than psychopathogenesis, it is very difficult

to “test” the validity of our primary objective. In other words, we know very little about the biologic substrates of anxiety in the two groups of boys, and consensus-based criteria for what constitutes clinically relevant differences are for the most part nonexistent.

Clinical implications

If one accepts the idea that etiology is the ideal basis for nosology and that treatments are validated for specific disorders, then our results have several clinical implications. First, we have expanded the Robbins and Guze (1970) criteria for diagnostic validity to include the pathogenesis of associated features (i.e., co-occurring symptomatology). Second, different processes appear to be at work for different types of anxiety. Moreover, the two groups of boys in this study appear to have different clinical presentations. Although this study focused on fairly molar psychosocial variables and measures of co-occurring symptoms, it nevertheless speaks to the broader issue of heterogeneity within clinical phenotypes, which is a serious stumbling block in the molecular genetics of neurobehavioral syndromes (e.g., Belmonte et al. 2004; Meyer-Lindenberg and Weinberger 2006; Szatmari et al. 2007; Abrahams and Geschwind, 2008). The picture is further complicated by the fact that genetic effects are often pleiotropic, as evidenced by the fact that the same gene may play a causal role in ADHD, anxiety, and/or tics (e.g., Comings et al. 1996; Gadow et al. 2008a). Because anxiety and, presumably, tics are highly responsive to environmental variables, which are themselves often nonspecific (e.g., Goodman et al. 1998), fully realized pathogenic models of these disorders and their co-occurrence will need to embrace gene \times environment pleiotropy.

In this study, tic severity was clearly associated with severity of co-occurring anxiety (and this was true for both parent and teacher ratings). One possible explanation for the interrelation of anxiety and tic severity is that they are both exacerbated by the same stimuli, and individuals with CMTD are differentially more sensitive to these stimuli. However, few studies have actually investigated the relation of life events, psychosocial stressors, or emotional stimuli with tic severity (e.g., Findley et al. 2003; Wood et al. 2003; Hoekstra et al. 2004a), their biologic substrates, or their relation to comparable processes involved in anxiety induction or the pathogenesis of anxiety disorders.

Disclosures

Drs. Gadow and Sprafkin are shareholders in Checkmate Plus, publishers of the *Child Symptom Inventory-4*, a behavior rating used in this study. Drs. Schneider and Crowell have no financial ties or conflicts of interest to report.

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Address correspondence to:

Jayne Schneider, Ph.D.

Department of Psychiatry and Behavioral Science

Putnam Hall, South Campus

State University of New York

Stony Brook, NY 11794-8790

E-mail: jayne.schneider@stonybrook.edu