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Anxiety Disorders in Children and Their Families

Cynthia G. Last, PhD; Michel Hersen, PhD; Alan Kazdin, PhD; Helen Orvaschel, PhD; Sean Perrin, MS

● The first- and second-degree relatives of children with anxiety disorders were compared with relatives of children with attention deficit-hyperactivity disorder and children who had never been psychiatrically ill for lifetime rates of psychopathological conditions, particularly anxiety disorders. Results from blind, diagnostic interviews indicated an increased prevalence of anxiety disorders in the first-degree relatives of children with anxiety disorder compared with relatives of both children with attention deficit-hyperactivity disorder and never psychiatrically ill children. Relationships between specific anxiety disorders in children and their relatives revealed an increased rate of panic disorder among the first-degree relatives of children with over-anxious disorder, compared with the relatives of children with separation anxiety disorder and children with other types of anxiety disorders. There also was a trend for panic disorder to be more prevalent among relatives of children with panic disorder than among relatives of children with anxiety disorder without panic. Obsessive-compulsive disorder was the only other anxiety disorder that appeared to show a similar specific relationship between children and their relatives. In general, the findings from this study suggest that there is a familial component involved in the pathogenesis of childhood anxiety disorders. The specificity of this relationship varies among individual anxiety disorders.

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In recent years, childhood anxiety disorders have gained increased attention from the research community. The *DSM-III-R* includes three anxiety disorders in the childhood section of the manual (separation anxiety disorder [SAD], overanxious disorder [OAD], and avoidant disorder), and five additional anxiety disorders (phobic disorder, panic disorder, generalized anxiety disorder, obsessive-compulsive disorder [OCD], and posttraumatic stress disorder [PTSD]) that may be applied to children as well as adults. In a series of studies by Last and colleagues,¹⁻⁶ preliminary data have been presented supporting the validity of many of these specific anxiety disorder diagnoses in children. However, concerns still remain regarding the ad-

equacy of our current classification system for diagnosing anxiety disorders in childhood populations.⁷

One important type of investigation that can be useful for validating diagnostic categories is the family study.⁸ If children with diagnosable *DSM-III-R* anxiety disorders show a higher prevalence of such disorders among their relatives (than the relatives of children without *DSM-III-R* anxiety disorders), such findings would lend support for the validity of our current diagnostic scheme. In addition to serving as validating indicators for diagnostic categories, family studies also provide information helpful for identifying risk factors involved in the pathogenesis of psychiatric disorders. Such information may assist in efforts toward prevention and early detection and also may be useful in formulating hypotheses regarding optimal treatment strategies.

Unfortunately, to date only one family study has been conducted with a large number ($n=58$) of children with anxiety disorder using blind direct interview procedures.¹ In this study, Last and colleagues compared lifetime psychiatric illness for mothers of children with anxiety disorder and mothers of children with behavior disorder. Results indicated an increased prevalence of anxiety disorders in the mothers of children with anxiety disorder relative to mothers in the psychopathological control group. No differences were observed between the two groups for any other psychiatric illness. Unfortunately, this study was limited to assessing psychiatric illness in mothers only and therefore did not provide a complete picture of familial aggregation.

In the current study, we expand on our previous research by using a similar method to assess lifetime psychiatric illness, particularly anxiety disorders, in all first- and second-degree relatives of a new, independent sample of children with anxiety disorder. Relatives of children with anxiety disorder were compared with relatives from two control groups of children: a psychopathological control group (attention deficit-hyperactivity disorder [ADHD]), included to control for the effects of psychopathological conditions per se, and a never psychiatrically ill (NPI) control group, included to obtain base rates for the particular psychiatric illnesses of interest. To our knowledge, our investigation is the first controlled study using blind, direct interviews to assess psychiatric illness in the families of children with anxiety disorder.

SUBJECTS AND METHODS

Recruitment

Probands included 94 children with an anxiety disorder, 58 children with ADHD, and 87 NPI children. Probands with anxiety disorder were recruited from the Child and Adolescent

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Anxiety Disorder Clinic (CAADC) at Western Psychiatric Institute and Clinic (WPIC), University of Pittsburgh (Pa) School of Medicine, during 3 consecutive years. The CAADC is an outpatient specialty clinic that evaluates and treats school-age children (5 to 18 years) with anxiety disorders. Children are referred to the CAADC through the triage service of WPIC, which conducts extensive telephone screenings of all patients new to the facility. Following these preliminary screenings, patients who were suspected of having anxiety problems were scheduled for intake evaluations at our clinic. In addition, patients who were scheduled for intake assessments at one of the other child clinics (because telephone screening was negative for anxiety), but on intake were discovered to have anxiety disorders, were subsequently transferred to our clinic for further evaluation and/or treatment. In this way, we ensured that our specialty clinic came into contact with all children with anxiety disorder entering the WPIC system.

Following diagnostic evaluation at our clinic (see below), participation was offered to families of children with anxiety disorder if children met the following criteria: (1) *DSM-III-R* diagnosis of an anxiety disorder, (2) no history of ADHD, and (3) currently residing with at least one biological parent. During the 3-year period of the study, the CAADC assessed 174 children with anxiety disorder. Of the 174, 24 (13.8%) did not meet the second or third inclusion criteria (17 had ADHD and seven were not residing with at least one biological parent), 53 (30.5%) refused participation, and three (1.7%) dropped out of the study, leaving a sample size of 94.

Probands with ADHD were recruited during the same period as probands with anxiety disorder from the general child outpatient clinic at WPIC. Participation was offered to the families of these children if they met the following criteria: (1) *DSM-III-R* diagnosis of ADHD, (2) no history of an anxiety or affective disorder, and (3) currently residing with at least one biological parent. Of 207 children with ADHD screened during the study period, 69 (33.3%) did not meet the second or third inclusion criteria (31 had anxiety disorder, nine had depressive disorder, and 29 were not residing with at least one biological parent), and 80 (38.6%) refused or did not respond to our requests (letters and telephone calls) to participate, leaving a sample size of 58.

Never psychiatrically ill probands were recruited from the Pittsburgh community and surrounding areas via mailings utilizing Cole's directory. Participation was offered to the families if children met the following criteria: (1) no history of any psychiatric disorder, (2) no history of mental health contact, and (3) currently residing with at least one biological parent. Probands in the NPI group were matched as closely as possible for age and sex to the probands with anxiety disorders.

Proband Diagnostic Procedures

All 239 children in the study were administered an unpublished, modified version of the Schedule for Affective Disorders and Schizophrenia for School-age Children (Present Episode; K-SADS; J. Puig-Antich, MD, W. J. Chambers, MD, 1978) to determine whether they met inclusion criteria for the study. This version of the K-SADS was modified by one of us (C.G.L.) in 1986 to include comprehensive sections on all *DSM-III-R* anxiety disorders, using rating scales based on *DSM-III-R* criteria. In addition, the modified interview schedule covers past as well as current psychopathological conditions. The interview was administered to parents and their children by a trained clinical child psychologist. Interrater diagnostic agreement was obtained for 156 (65%) of the 239 probands by having a second interviewer score audiotapes of the interviews. The κ coefficients of agreement for any anxiety disorder, ADHD, and no psychiatric disorder were 1.00, .98, and 1.00, respectively. The κ coefficients for specific anxiety disorder diagnoses for probands with anxiety disorder were as follows: SAD, .94; OAD, .93; avoidant disorder, .74; panic disorder, .88; social phobia, .94; simple phobia, .71; OCD, .78; and PTSD, 1.00. In the few instances where the two interviewers disagreed in regard to specific diagnoses, the diagnosis of the "live" interviewer was utilized.

Of the 94 probands with anxiety disorder, 45 (48%) presented with one anxiety disorder, and 49 (52%) had a history of multiple anxiety disorders. The frequency of anxiety disorder diagnoses among children with one anxiety disorder was as follows: SAD, 14; simple phobia, eight; panic disorder (with or without agoraphobia), seven; social phobia, six; OCD, five; PTSD, two; OAD, one; avoidant disorder, one; and anxiety disorder not otherwise specified, one. For children with multiple anxiety disorders, three quarters (36) received diagnoses of OAD (16), SAD (14), or both OAD and SAD (six). The remaining 13 children with multiple anxiety disorders had primary diagnoses of PTSD (four), OCD (three), panic disorder (two), social phobia (two), simple phobia (one), and agoraphobia without a history of panic disorder (one). Major depression was present in the history of 19 (20%) of the children and adolescents with anxiety disorder. In the ADHD group, 19 of the probands (33%) showed a history of conduct or oppositional disorder.

Information on the severity and duration of primary anxiety disorders for the probands with anxiety disorder was obtained at the time of the diagnostic interview. Severity was rated by the interviewer using a four-point Likert-type scale that ranged from 1 to 4 (1 being mild; 2, moderate; 3, severe; and 4, extreme). Anchor points for the severity scale were based on both symptoms and impairment. Most of the children received a rating of 2 (moderate) or 3 (severe) for their primary anxiety disorder (9.6% had a rating of 1; 38.3%, 2; 35.1%, 3; and 17.0%, 4). The mean (\pm SD) rating for the group was 2.6 ± 0.88 and the median rating was 3.0. Duration of primary anxiety disorder at intake ranged from 2 weeks to 11.77 years, with a mean of 2.42 ± 2.37 years and a median of 1.12 years.

Family Diagnostic Procedures

First-degree relatives included mothers (anxiety, $n=94$; ADHD, $n=58$; NPI, $n=87$), fathers (anxiety, $n=94$; ADHD, $n=58$; NPI, $n=86$), and full siblings, 5 years of age or older (anxiety, $n=86$; ADHD, $n=36$; NPI, $n=67$). Available first-degree relatives were interviewed directly using the family study method. Adult first-degree relatives (18 years of age or older) were interviewed for current and past psychiatric illness with the Structured Clinical Interview for *DSM-III-R*, Nonpatient Version (SCID) (R. L. Spitzer, MD, J. B. W. Williams, DSW, M. Gibbon, MSW, 1986). Childhood disorders not contained in the SCID (ie, SAD, OAD, avoidant disorder, and ADHD) also were administered to the adult relatives using sections from the modified K-SADS. Child and adolescent full siblings were interviewed for current and past psychiatric illness with the modified K-SADS. In addition to direct interviews, spouses were asked to report on each other using the family history method.⁹ For first-degree relatives who were not available or refused direct interview, the family history method alone was utilized.

Almost all (95% to 96%) of the mothers in each of the three groups were administered direct interviews. For fathers, direct interviews were administered to 38% (36) of those whose children were in the group with anxiety disorder, 35% (20) of the ADHD group, and 56% (48) of the NPI group (anxiety vs NPI, $P<.05$; ADHD vs NPI, $P<.05$). The smaller percentage of fathers directly interviewed in the two patient groups in part reflected the greater percentages of divorced or separated parents (see "Sociodemographic Characteristics" section below) in these groups (divorced or separated mothers usually were reluctant or refused to have fathers contacted to participate in the study). Approximately three quarters (75% to 79%) of the full siblings in each of the three groups were interviewed directly.

Information on second-degree relatives (maternal and paternal grandparents, aunts, and uncles) (anxiety, $n=812$; ADHD, $n=484$; NPI, $n=718$) was obtained from the parents using the family history method. Mothers were asked to report on their own relatives and the father's relatives. Fathers also were asked to report on their own relatives.

All family interviews were conducted by a psychologist who was trained in the administration of the SCID, the modified

K-SADS, and the family history method and who was "blind" to probands' diagnoses. The interviewer assigned all applicable DSM-III-R diagnoses to each family member based on all available interview data. In instances where there were multiple informants for a given family member, the information was integrated by the clinician to formulate a final diagnosis. When information provided by the informants was discrepant, the clinician was instructed to assign the most psychopathological or severe disorders (for example, major depression rather than dysthymia), unless clinical judgment indicated that a particular informant's report was clearly invalid.

Interrater diagnostic agreement was obtained by having a second clinician independently score audiotapes from 95 (40%) complete families (1178 individual interviews) and assign DSM-III-R diagnoses. The κ coefficients of agreement between the two clinicians for any anxiety disorder, major depression, alcohol dependence, and drug dependence were .95, .92, .99, and .97, respectively. The κ coefficients for specific anxiety disorders were as follows: generalized anxiety disorder, 1.00; panic disorder, .86; simple phobia, .95; social phobia, .96; OCD, .86; PTSD, .96; SAD, .91; avoidant disorder, .89; and OAD, .93.

Sociodemographic Characteristics

The mean ages of the proband groups were 12.2 ± 3.6 years for children with anxiety disorder (range, 5 to 18 years), 8.9 ± 2.4 years for children with ADHD (range, 5 to 10 years), and 11.0 ± 3.5 years for NPI children (range, 5 to 18 years; $P < .0001$). The sex distribution of the groups was as follows: anxiety disorder, 49% male, 51% female; ADHD, 84% male, 16% female; NPI, 43% male, 57% female ($P < .0001$). As expected, pairwise comparisons indicated that children with ADHD differed significantly from the other two groups for age (vs anxiety, $P < .0001$; vs NPI, $P < .001$) and sex (vs anxiety, $P < .0005$; vs NPI, $P < .0001$). Examination of the marital status of the families in each of the three groups showed that the two patient groups contained a greater percentage of divorced or separated parents compared with the NPI group (anxiety, 37%; ADHD, 38%; NPI, 20%; overall, $P < .05$; anxiety vs NPI, $P < .05$; ADHD vs NPI, $P < .05$). Finally, examination of the socioeconomic status of the families of the children indicated that the ADHD group differed from the NPI group in social strata ratings (Hollingshead strata IV and V, anxiety, 41%; ADHD, 55%; NPI, 34%; overall, $P < .05$; ADHD vs NPI, $P < .05$).

Data Analysis

Rates of illness are reported as observed lifetime prevalences. Because first- and second-degree relatives in all three groups were in the period of risk for anxiety disorders, we elected to present observed (raw) vs age-corrected rates. Reanalysis with the Weinberg shorter method of age correction¹⁰ yielded similar patterns of findings but with grossly inflated percentages.

The statistical significance of differences between rates of disorder were assessed using 2×2 χ^2 tests with Yates' correction for continuity or Fisher's Exact tests.

RESULTS

Prevalences for Anxiety Disorders

Rates of anxiety disorders for first-degree relatives by relationship and sex are presented in Table 1. An increased rate of anxiety disorders was found in first-degree relatives of probands with anxiety disorder compared with first-degree relatives of both probands with ADHD and NPI probands. Looking at the relationship and sex of relative, the data suggest that significant differences obtained for rates of anxiety disorders for parents and siblings of probands with anxiety disorder were due, primarily, to differences among male, as opposed to female, relatives. The rate of anxiety disorders for male relatives (fathers and brothers) of probands with anxiety disorder was significantly higher than rates obtained for both the ADHD and NPI groups. Rates for female first-degree relatives (mothers and sisters) did not differ for probands with anxiety disorder and

Table 1.—Rates of Anxiety Disorders in First-Degree Relatives of Children With Anxiety Disorder (n = 94), With ADHD (n = 58), and NPI Children (n = 87)*

Group	Proband Diagnosis		
	Anxiety	ADHD	NPI
All first-degree relatives	34.6†‡	23.5	16.3
Parents	40.4†‡	28.3§	18.5
Siblings	21.7	8.3	10.8
M relatives	23.9†¶	10.5	8.0
F relatives	45.5¶	37.0§	24.2

*ADHD indicates attention deficit-hyperactivity disorder; NPI, never psychiatrically ill. Probabilities are based on χ^2 tests with Yates' correction for continuity or Fisher's Exact tests. Rates are unadjusted. Sample sizes for relatives of children with anxiety disorder, with ADHD, and NPI children, respectively, were as follows: all first-degree relatives, 274, 152, and 240; parents, 188, 116, and 173; siblings, 86, 36, and 67; males, 141, 79, and 120; and females, 133, 73, and 120.

† $P < .05$ vs ADHD.

‡ $P < .10$ vs ADHD.

¶ $P < .00001$ vs NPI.

§ $P < .001$ vs NPI.

|| $P < .10$ vs NPI.

ADHD, but both of these groups showed significantly elevated rates compared with the NPI group. Comparison of second-degree relatives did not show differences between the anxiety (11.5%) and ADHD (11.0%) groups, but both of these patient groups differed significantly from the NPI group (7.3%; anxiety vs NPI, $P < .01$; ADHD vs NPI, $P < .05$).

For first-degree relatives, significant differences observed for rates of anxiety disorders between the group with anxiety disorders and the two control groups were due in large part to differences obtained for male relatives (fathers and brothers). Since we had a relatively poor showing for fathers in all three proband groups, in many cases fathers were diagnosed based exclusively on indirect interview data obtained from mothers. Thus, it would be reasonable to question whether our differences for male relatives would have held up had the data set consisted of direct interviews only. To address this issue, we reconducted the above analyses excluding fathers who had not been directly interviewed. Findings from the reduced sample yielded results that were identical, in terms of statistical significance, to results obtained from the original analyses (results of these reanalyses are available on request).

Because of current controversy surrounding the validity of the DSM-III-R classification of OCD and PTSD as anxiety disorders, we repeated the above analyses by excluding probands with anxiety disorder who had OCD and/or PTSD only ($n = 7$) and excluding OCD and PTSD in relatives in our rates of anxiety disorder. In other words, analyses were recalculated excluding OCD and PTSD as anxiety disorders. Results from our reanalyses were virtually identical (in regard to percentages and statistical significance) to findings from the original analyses (available on request).

Age at Onset and Treatment for Anxiety Disorders

Age-at-onset and treatment data for relatives were collected at the time of the diagnostic interview. For age at onset of earliest anxiety disorder, female first-degree relatives were similar across the three groups (anxiety, 12.8; ADHD, 11.4; NPI, 11.7). There was a suggestion that male first-degree relatives of children with anxiety disorder had an earlier age at onset for anxiety disorder than male first-degree relatives of children with ADHD (anxiety, 9.5; ADHD, 13.4; NPI, 12.8; anxiety vs ADHD, $P < .10$). Relatively few of the first-degree relatives with anxiety disorder received treatment for their anxiety disorders (female: anxiety, 20.3%; ADHD, 13.8%; NPI, 3.7%; male: anxiety, 12.5%; ADHD, 14.3%; NPI, 9.1%), with no significant differences between the groups.

Table 2.—Rates of Specific Anxiety Disorders in First-Degree Relatives of Children With Anxiety Disorder (n=94), With ADHD (n=58), and NPI Children (n=87)*

Relatives' Diagnoses	Proband Diagnosis		
	Anxiety	ADHD	NPI
Panic disorder (with or without agoraphobia)	4.9†	2.0	0.4
Social phobia	8.7‡	7.4	3.4
Simple phobia	11.7†§	4.7	4.3
Obsessive-compulsive disorder	2.3‡	2.0	0.0
Generalized anxiety disorder	2.7	2.0	0.9
Posttraumatic stress disorder	5.0	7.4	3.1
Separation anxiety disorder	9.2	5.6	4.3
Overanxious disorder	18.9§¶	10.3	8.1
Avoidant disorder	5.9†	4.0	1.5

*ADHD indicates attention deficit-hyperactivity disorder; NPI, never psychiatrically ill. Probabilities are based on χ^2 tests with Yates' correction for continuity or Fisher's Exact tests. Rates are unadjusted. Sample sizes for relatives of the three groups were 274 (anxiety disorder), 152 (ADHD), and 240 (NPI).

† $P < .005$ vs NPI.

|| $P < .10$ vs NPI.

‡ $P < .05$ vs NPI.

¶ $P < .001$ vs NPI.

§ $P < .05$ vs ADHD.

Table 3.—Rates of Specific Anxiety Disorders in First-Degree Relatives of Probands With SAD (n=28), OAD (n=17), and Other Anxiety Disorders (n=43)*

Relatives' Diagnoses	Proband Diagnosis		
	SAD	OAD	Other
Any anxiety disorder	31.5	50.0†‡	27.0
SAD	10.3§	18.8‡	3.4
OAD	23.7	29.8¶	11.0
Panic disorder (with or without agoraphobia)	2.7	11.5‡#	0.0
Generalized anxiety disorder	4.2	3.8	0.8

*SAD indicates separation anxiety disorder; OAD, overanxious disorder. Probabilities are based on χ^2 tests with Yates' correction for continuity or Fisher's Exact tests. Rates are unadjusted. Sample sizes for relatives of the three groups were 74 (SAD), 54 (OAD), and 130 (other). Six probands with both SAD and OAD have been excluded from these analyses. The 35 relatives of nine children with panic disorder were eliminated from the group with other anxiety disorders for the analysis of panic disorder.

† $P < .10$ vs SAD.

|| $P < .05$ vs other.

‡ $P < .005$ vs other.

¶ $P < .01$ vs other.

§ $P < .10$ vs other.

$P < .05$ vs SAD.

We had hypothesized that children with anxiety disorder with an earlier age at onset (<12 years) for anxiety disorder would show higher rates of anxiety disorders in their families. Comparison of the first-degree relatives of younger (n=74) and older (n=20) probands with anxiety disorder did not support this prediction, with similar rates of anxiety disorders appearing in both groups.

Anxiety Disorders Within Families

Although prevalences provide useful information, they give little indication about how anxiety disorders may aggregate within families. To examine this, we used individual families as the unit of analysis and compared the three groups on the (1) number (percentage) of families containing a first-degree relative with an anxiety disorder, (2) number (percentage) of families containing a parent with an anxiety disorder, and (3) number

(percentage) of families containing a sibling with an anxiety disorder. The percentage of families having at least one first-degree relative with an anxiety disorder was as follows: anxiety, 69.9%; ADHD, 50.0%; and NPI, 40.5%; differences between the anxiety and ADHD groups, and the anxiety and NPI groups, were statistically significant ($P < .05$ and $P < .0005$, respectively). The percentage of families having at least one parent with an anxiety disorder was as follows: anxiety, 65.6%; ADHD, 50.0%; and NPI, 35.7%; comparison of the anxiety and NPI groups yielded a significant difference ($P < .0001$), while comparison of the anxiety and ADHD groups showed a trend toward statistical significance ($P < .10$). The pattern of results for siblings was in the expected direction, but nonsignificant: anxiety, 26.3%; ADHD, 10.7%; and NPI, 13.6%.

Specific Anxiety Disorders in Relatives

Prevalences for specific anxiety disorders in the first-degree relatives of probands in each of the three groups are presented in Table 2. As indicated, simple phobia and OAD were the two specific anxiety disorders that were most frequent among the relatives of probands with anxiety disorder; these rates were significantly higher than rates obtained for the two disorders for both the ADHD and NPI group relatives. Panic disorder (with or without agoraphobia), social phobia, OCD, and avoidant disorder were more prevalent among the first-degree relatives of probands with anxiety disorder than NPI probands, but no differences emerged between the two patient groups for any of these disorders. A trend toward statistical significance emerged when comparing the anxiety and control groups for the prevalence of SAD. There were no differences among the three groups of relatives for generalized anxiety disorder. For relatives of probands with ADHD, rates of OCD, PTSD, and avoidant disorder showed trends toward statistical significance when compared with rates obtained for the relatives of NPI probands, but no differences emerged between the two patient groups for any of these disorders.

Rates for specific anxiety disorders also were compared, separately, for first-degree male and female relatives of probands in the three groups. For first-degree male relatives, simple phobia (anxiety, 7.6%; ADHD, 1.3%; NPI, 0.9%), SAD (anxiety, 8.4%; ADHD, 1.9%; NPI, 1.1%), and OAD (anxiety, 14.7%; ADHD, 1.9%; NPI, 5.4%) were more prevalent in relatives of probands with anxiety disorder than relatives in both of the other two groups (simple phobia: anxiety vs ADHD, $P < .05$, anxiety vs NPI, $P < .01$; SAD: anxiety vs ADHD, $P < .10$, anxiety vs NPI, $P < .05$; OAD: anxiety vs ADHD, $P < .001$, anxiety vs NPI, $P < .05$). No other differences emerged among the groups.

By contrast, for first-degree female relatives, there were no differences between the anxiety and ADHD groups for any of the specific anxiety disorders. Each of the anxiety disorders, with the exception of generalized anxiety disorder, PTSD, and SAD, was more prevalent among the female first-degree relatives of probands with anxiety disorder than among the female first-degree relatives of NPI probands (panic disorder, $P < .005$; social phobia, $P < .05$; simple phobia, $P < .10$; OCD, $P < .05$; OAD, $P < .05$; avoidant disorder, $P < .001$). The relatives of probands with ADHD showed higher rates of PTSD ($P < .05$) and avoidant disorder ($P < .01$) than relatives of NPI probands.

Relationship Between Probands' and Relatives' Anxiety Disorders

A priori, we had hypothesized that specific anxiety disorders in our child probands would be associated with specific anxiety disorders in the children's relatives. More specifically, we had hypothesized that the rates of SAD and panic disorder would be highest for the relatives of probands with SAD, and that OAD and generalized anxiety disorder would be more prevalent among the relatives of probands with OAD. To examine these issues, we compared the first-degree relatives of three groups of children with anxiety disorder—those with SAD but not OAD, those with OAD but not SAD, and those with an anxiety disorder

Table 4. — Rates for Other Psychiatric Disorders in First- and Second-Degree Relatives of Children With Anxiety Disorder (n = 94), With ADHD (n = 58), and NPI Children (n = 87)*

Relatives' Diagnoses	Proband Diagnosis		
	Anxiety	ADHD	NPI
Major depression			
First-degree	23.7†	22.3	16.5
Second-degree	10.2‡§	6.3	6.0
Alcohol dependence			
First-degree	20.0§	23.6	10.8
Second-degree	18.0§	21.3¶	12.8
Drug dependence			
First-degree	10.3#	13.5**	4.8
Second-degree	6.6§	8.6	3.5

*ADHD indicates attention deficit–hyperactivity disorder; NPI, never psychiatrically ill. Probabilities are based on χ^2 tests with Yates' correction for continuity. Rates are unadjusted. Sample sizes for relatives of children with anxiety disorder, with ADHD, and NPI children, respectively, were as follows: first-degree, 274, 152, and 240; second-degree, 812, 484, and 718.

† $P < .10$ vs NPI.

‡ $P < .05$ vs ADHD.

§ $P < .01$ vs NPI.

|| $P < .001$ vs NPI.

¶ $P < .0005$ vs NPI.

$P < .05$ vs NPI.

** $P < .005$ vs NPI.

der other than SAD or OAD (anxiety controls)—for rates of SAD, panic disorder, OAD, and generalized anxiety disorder.

As indicated in Table 3, contrary to expectation, SAD was more prevalent among the relatives of both probands with SAD and probands with OAD (compared with the relatives of probands with other anxiety disorders), and panic disorder was highest in relatives of probands with OAD (compared with relatives in each of the other two groups). Again, contrary to expectation, OAD was more prevalent among the relatives of both probands with SAD and probands with OAD (compared with relatives of probands with other anxiety disorders), and no differences emerged among any of the three groups of relatives for generalized anxiety disorder.

As indicated in Table 3, prevalences for "any anxiety disorder" showed relatives of probands with OAD to have the highest rate compared with rates obtained in each of the other two groups. Examination of major depression among the three groups of relatives revealed only one significant difference: the relatives of probands with SAD had a higher rate of major depression than the relatives of probands with other anxiety disorders (SAD, 29.2%; OAD, 25.0%; other anxiety disorders, 16.1%; SAD vs other, $P < .05$).

We also investigated the relationship between other specific anxiety disorders in children and their relatives. Obsessive-compulsive disorder and panic disorder were the only two anxiety disorders that showed a suggestion of a specific relationship in children and their relatives. The rate of OCD in the first-degree relatives ($n = 47$) of children with OCD ($n = 14$) was somewhat higher than the rate obtained for relatives of probands with anxiety disorder without OCD (6.7% vs 1.4%; $P < .10$). Similar findings were obtained when comparing relatives ($n = 39$) of children with panic disorder ($n = 13$) with relatives of probands with anxiety disorder without panic disorder (10.8% vs 3.9%; $P < .10$). Additional analyses for social phobia, simple phobia, avoidant disorder, and PTSD did not yield significant differences or trends toward significance.

Relatives of Depressed and Nondepressed Probands With Anxiety Disorder

The first-degree relatives of two groups of probands with anxiety disorder—those with a history of any depressive disorder (major depression, dysthymia, or depressive disorder not oth-

erwise specified; $n = 25$) and those without a history of any depressive disorder ($n = 69$)—were compared for rates of anxiety and depressive disorders. Contrary to expectation, no differences emerged in rates of any depressive disorder or major depression for the two groups of relatives. Rates of anxiety disorders (any type) also did not differentiate the two groups.

Multiple Anxiety Disorders

We had hypothesized that the relatives of probands with multiple (more than one) anxiety disorders would differ in two ways from relatives of probands with only one anxiety disorder: (1) the former group would show a higher rate of anxiety disorders among relatives, and (2) the former group would show a larger percentage of relatives with a history of multiple anxiety disorders. Prediction 1 was not supported. The rates of anxiety disorders among the first-degree relatives of both groups of probands with anxiety disorder were comparable. For prediction 2, there was a trend toward statistical significance in the expected direction (59.6% vs 37.1%; $P < .10$). Probands with multiple anxiety disorders did not differ in age from probands with only one anxiety disorder; similarly, relatives with multiple anxiety disorders did not differ in age from relatives with only one anxiety disorder. Among first-degree relatives with a history of at least one anxiety disorder, 51.1% of the anxiety group, 51.4% of the ADHD group, and 34.3% of the NPI group showed multiple anxiety disorders (not significant).

Reanalysis for Sociodemographic Differences Among Probands

Sociodemographic differences observed between children with ADHD and children with anxiety disorder in the study are consistent with previous research on the clinical characteristics of populations with ADHD.¹¹ More specifically, children with ADHD tended to be predominantly male, young, and from low socioeconomic strata. To address empirically whether any of these sociodemographic differences affected findings from our study, a series of reanalyses were conducted. Given that the ADHD group had virtually no variability (heterogeneity) for age and sex (almost all younger and male), it was not possible to employ logistic regression procedures to assess the effects of these variables on our data set. Thus, we employed an alternative strategy: rates of anxiety disorder were recalculated and compared for male probands (in all three groups) only, and, in addition, rates were recalculated and compared for younger probands (<13 years) only. Findings from the reduced samples were similar to results obtained for the original analyses (available on request). To address the possible role of socioeconomic status differences on our findings, we compared families with high vs low socioeconomic status for rates of anxiety disorder. Here no relationship was observed between social status ratings and the presence or absence of anxiety disorder (available on request).

Sex Differences for Anxiety Disorders

As expected from previous findings in this area,¹² statistically significant sex differences for anxiety disorders were found. The rates of anxiety disorders among the first-degree female relatives of each of the three groups of probands were higher than rates observed for first-degree male relatives (anxiety, 46% vs 24%, $P < .0005$; ADHD, 37% vs 11%, $P < .0005$; NPI, 24% vs 8%, $P < .005$). For second-degree relatives, differences between male and female relatives reached statistical significance only for the ADHD group, with a trend for the NPI group (anxiety, 13% vs 10%, not significant; ADHD, 15% vs 6%, $P < .01$; NPI, 9% vs 5%, $P < .10$).

Other Psychiatric Disorders in Relatives

The rates of other psychiatric disorders (major depression, alcohol dependence, drug dependence) thought to be related to anxiety disorders were compared in first- and second-degree

relatives of probands with anxiety disorder, ADHD, and NPI. As indicated in Table 4, there was some suggestion of a greater prevalence of major depression among the relatives, particularly second-degree, of probands with anxiety disorder. An increased risk of both alcohol and drug dependence was observed for the first- and second-degree relatives of probands with anxiety disorder and ADHD compared with the relatives of NPI probands. The two patient groups did not differ significantly from each other for substance dependence.

Because the families of children with ADHD served as psychopathological controls in this study, we were interested in observing the rates of ADHD in the three groups of relatives, particularly for the males. However, given the small number of fathers who were interviewed directly, and because adult informants often were unable to report on the occurrence of this childhood-onset disorder in their spouses and their parents, morbidity risks could not be calculated for fathers and second-degree male relatives. Rates were calculated for male siblings and showed a higher prevalence of ADHD for the brothers of probands with ADHD (24%) compared with the brothers of probands with anxiety disorder (6%) and NPI probands (3%; both $P < .05$).

COMMENT

Findings from this family study showed significantly higher rates of anxiety disorders in the first-degree relatives of children with anxiety disorder compared with relatives of both children with ADHD and NPI controls. Differences for first-degree male relatives particularly were striking; male relatives of children with anxiety disorder had a rate of anxiety disorders more than twice that of the other two groups. Inspection of the specific types of anxiety disorders among male relatives showed elevated rates of SAD, OAD, and simple phobia. For first-degree female relatives, the anxiety disorder group significantly differed in rates of anxiety disorder from the normal control group but not the psychopathological control group. Additional analyses with individual families as the unit of analysis also revealed that anxiety disorders were more likely to aggregate within families of children with anxiety disorder than within families of both children with ADHD and NPI children.

The lack of significant findings for anxiety disorders for second-degree relatives warrants comment. Information on second-degree relatives relied exclusively on the family history method (ie, the child's parents reported on all second-degree relatives), which has been shown to underestimate psychopathological conditions, particularly anxiety disorders.⁹ However, while rates of anxiety disorders for these relatives were likely underestimated, each of the three groups should have been affected equally by this underrepresentation. In other words, the potential pattern of differences should not have been affected by the use of the family history method. Alternatively, it is possible that the use of this method with relatives who have not been living with the informant for quite some time (the informant's parents, sisters, and brothers) yields reduced validity. Previous research in this area has shown that "closeness" (for example, spouses reporting on each other) increases the validity of the assessment technique.⁹

Our prediction about the relationship between childhood SAD and adult-onset panic disorder was not supported in the present study. Weissman et al¹³ found an increased risk of SAD in the offspring of mothers with comorbid depressive and panic disorders. By contrast, we found an increased risk of panic disorder in the relatives of children with panic disorder or OAD, but not children with SAD. Since our findings on the relationship for SAD

and panic disorder were presented for all first-degree relatives, data were reanalyzed for mothers only (more akin to the Weissman et al analysis); we again failed to find a relationship between the two disorders.

Discrepancies in the findings from the two studies may be due to methodological differences. First, in the Weissman et al investigation, all of the probands had concurrent depressive disorder. Second, their study observed illness in the offspring of disordered adults, while we observed illness in relatives of disordered children. Finally, the Weissman et al investigation used the family history method rather than the family study method to diagnose offspring.

In addition to the prevalence of panic disorder, the relatives of children with OAD had a higher rate of anxiety disorders (50%) in general than relatives of children with SAD (32%) or children with other anxiety disorders (27%). In fact, the relatives of children with OAD had the highest rate of anxiety disorders of any of the specific anxiety disorder proband groups in our study (other specific anxiety disorders ranged from 31% to 37%). These findings are especially interesting in light of recent concerns expressed by other researchers in this area regarding the validity of this diagnostic category, and they support our previous research which suggests that OAD is a distinct and valid childhood anxiety disorder.³

There also was a trend for panic disorder to be more frequent in the relatives of children who had panic disorder. The same pattern held true for OCD (ie, a trend for OCD to be more frequent in the relatives of children with OCD), but not so for the other specific anxiety disorders. This specific relationship for panic disorder and OCD supports previous genetic research.¹⁴ Our findings for childhood OCD also are consistent with results from a recent uncontrolled family study of the disorder.¹⁵

The data for major depression among the first- and second-degree relatives of children with anxiety disorder were inconclusive. Other family studies have yielded conflicting findings on this subject,^{12,16-18} and it is evident that further studies are needed to clarify the familial relationship between anxiety and affective disorders. It should be noted that in our current study, few of our youngsters had a history of major depression. How this may have influenced our results is unclear, especially given the relatively young age of the children in relation to the period of risk for major depression.

Our finding of an increased risk of alcoholism for family members of children with anxiety disorder relative to normal controls is consistent with observations from family studies of adult patients with anxiety disorder.^{12,18-21} We also found an increased risk of drug dependence. Rates for substance dependence did not differ between the relatives of children with anxiety disorder and ADHD, which is not surprising given previous findings showing a strong association between childhood ADHD and a familial history of alcohol or drug dependence.^{22,23}

Although not the central focus of our study, rates of anxiety disorder observed in our study for the first-degree relatives of children with ADHD are interesting in light of recent data from other investigations. At the time our study was designed and initiated, ADHD was chosen as the psychopathological control group in large part because research up to that point had suggested that the overlap between ADHD and anxiety disorders in children was relatively minimal.¹¹ Family data from our study and

a recent study by Biederman et al,²⁴ which used similar methods, suggest that this may not be the case. We found a trend for elevated rates of anxiety disorder among female (but not male) first-degree relatives of children with ADHD compared with normal controls. Biederman et al found significantly elevated rates of anxiety disorder among the first-degree relatives of children with ADHD (18.6%) compared with normal controls (5.3%); unfortunately, data were not presented separately for male and female relatives, so it is not possible to determine whether our sex-specific finding existed in their sample as well. Using an alternative methodological approach, McClellan et al²⁵ conducted a family study that also suggests a relationship between ADHD and anxiety. In their study, the offspring of adult probands with panic disorder, major depression, or no psychiatric disorder were compared for rates of ADHD, anxiety disorder, and depression. Findings indicated that 15% of the offspring of adults with panic disorder had ADHD, and that ADHD in the child in most instances was comorbid with anxiety disorder and/or depression. Finally, support for comorbidity between ADHD and anxiety disorders also has arisen from a recent large-scale epidemiological study²⁶: 26% of children diagnosed as having anxiety disorder with depression met criteria for an anxiety disorder, and 24% of children diagnosed as having an anxiety disorder met criteria for ADHD.

We wish to point out some of the limitations of our investigation. First, our sample of children with anxiety disorder were clinically referred, and our findings are not, a priori, generalizable to the relatives of nonreferred (possibly less severely ill) children with anxiety disorder. Second, we had a relatively poor showing for fathers and thus relied on family history data in many instances, rather than the preferred method of direct interview. Confirmation of our findings for male first-degree relatives with a large group of interviewed fathers is warranted. Finally, many of our children with anxiety disorder showed multiple anxiety disorders, and some of the specific anxiety disorders were present in relatively few of the children. These factors limited our ability to evaluate specific relationships between the children's anxiety diagnoses and their relatives' diagnoses in a very clear fashion, although, at this time, our data certainly are suggestive of particular relationships.

Our findings suggest that there is a familial component involved in the pathogenesis of childhood anxiety disorders. The nature of this familial component, environmental and/or genetic, remains to be determined through genetic research and family interaction studies. Our findings also lend preliminary support for the validity of the *DSM-III-R* classification system for childhood anxiety disorders, although, certainly, additional research using alternative strategies is needed in this area. Longitudinal studies examining the stability of specific anxiety diagnostic groups is one such alternative strategy that our group currently is exploring.

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