Adoptive and Biological Families of Children and Adolescents With ADHD

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ABSTRACT

Objective: Using an adoption study design, the authors addressed the issue of genetics in attention-deficit hyperactivity disorder (ADHD). **Method:** This study examined the rates of ADHD and associated disorders in the first-degree adoptive relatives of 25 adopted probands with ADHD and compared them with those of the first-degree biological relatives of 101 nonadopted probands with ADHD and 50 nonadopted, non-ADHD control probands. **Results:** Six percent of the adoptive parents of adopted ADHD probands had ADHD compared with 18% of the biological parents of nonadopted ADHD probands and 3% of the biological parents of the control probands. **Conclusion:** Results of this study lend support to the hypothesis that ADHD has a genetic component. *J. Am. Acad. Child Adolesc. Psychiatry*, 2000, 39(11):1432–1437. **Key Words:** adoption, attention-deficit hyperactivity disorder, family study.

Attention-deficit hyperactivity disorder (ADHD) is a heterogeneous disorder that includes symptoms of inattention, hyperactivity, and impulsivity and is thought to affect at least 5% of school-age children (American Psychiatric Association, 1994). It is associated with high levels of morbidity and dysfunction (Biederman et al., 1992) and, while more common in males, it clearly affects females as well (Biederman et al., 1999; Gaub and Carlson, 1997). Follow-up findings have documented that the disorder persists into adolescence and adulthood in a substantial number of cases (Weiss, 1985).

Although its etiology remains unknown, data from family-genetic (Biederman et al., 1990, 1992), twin (Eaves et al., 1993; Goodman and Stevenson, 1989; Heffron et al., 1984; Lopez, 1965; Willerman, 1973), and segregation analysis (Faraone et al., 1992) studies strongly suggest a genetic etiology for this disorder. Despite variable nosological definitions, family studies have consistently documented that hyperactivity, *DSM-III* attention deficit disorder (ADD), and *DSM-III-R* ADHD aggregate in biological relatives of children with this disorder. In 2 double-blind, controlled, large-scale studies of *DSM-III* ADD and *DSM-III-R* ADHD, our group documented the familiality of the disorder (Biederman et al., 1990, 1992). Although *DSM-IV* studies of ADHD are not available, work by us (Biederman et al., 1997) and others has documented a large diagnostic overlap between *DSM-III-R* and *DSM-IV* definitions of the disorder, suggesting that *DSM-IV* ADHD is also very likely to be familial. Findings from a number of twin studies are consistent with a genetic hypothesis (Eaves et al., 1993; Goodman and Stevenson, 1989; Heffron et al., 1984; Lopez, 1965; Willerman, 1973) as are the results from a segregation analysis that suggested that ADHD may be the result of a single major gene with incomplete penetrance (Faraone et al., 1992). Furthermore, recent molecular genetic studies have reported compelling associations between ADHD and the dopamine transporter gene (Cook et al., 1995; Daly et al., 1998; Gill et al., 1997; Waldman et al., 1998) and the dopamine D4 receptor gene (Barr et al., 2000; Comings et al., 1999; Faraone et al., 1999; LaHoste et al., 1996; Rowe et al., 1998; Smalley et al., 1998; Swanson et al., 1998).

Adoption studies are another method that has been used to examine the genetics of disorders. Although the

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existing adoption studies generally support the hypothesis that there is a genetic contribution to the development of ADHD, the 3 adoption studies of ADHD published to date suffer from important methodological problems limiting interpretation of findings. Two of these studies were conducted in the 1970s (Cantwell, 1975; Morrison and Stewart, 1973) and used diagnostic definitions of the disorders that are quite different from the *DSM* definitions; the more recent study (Alberts-Corush et al., 1986) used mostly tests of cognition and vigilance and did not include operational criteria for diagnosis. Moreover, none of the studies blinded the assessments. This state of affairs calls for more research on this important subject.

To this end, this study was designed to address gaps in the scientific knowledge by conducting an adoption study of referred children with ADHD, using established operational definitions of the disorder and modern family study methodology. By comparing adopted and nonadopted ADHD probands, we were able to control for the effect that having a child with ADHD has on families. On the basis of the literature and our prior work, we hypothesized that the rates of ADHD and associated disorders in the adoptive relatives of the adopted ADHD probands would be lower than those found in the biological relatives of the nonadopted ADHD probands and similar to those observed in the biological relatives of the control probands.

METHOD

The adopted sample consisted of 25 white children of both genders in whom *DSM-III-R* ADHD had been diagnosed, between the ages of 5 and 18 years, adopted within the first year of life by a family of the same cultural background ("adopted ADHD") and their 62 first-degree adoptive relatives. The adopted ADHD group included 50 parents and 12 siblings. We included in the statistical analyses only siblings who were full biological children of the adoptive parents. Subjects were recruited from consecutive referrals to a pediatric psychopharmacology clinic at a major university center. For comparison, we used existing data from a pool of children with and without ADHD and their biological first-degree relatives assessed with an identical assessment battery referred to the same medical center as the adopted youths. These comparison samples consisted of 101 males and females in whom *DSM-III-R* ADHD had been diagnosed and who were not adopted ("biological ADHD") and 50 males and females who were referred from the pediatric clinics at the same major university center, did not meet criteria for ADHD, and were not adopted ("controls") and their 310 and 153 biological first-degree relatives, respectively. The biological ADHD group included 198 parents and 112 siblings, and the control group included 99 parents and 54 siblings. We selected nonadopted subjects to attain a similar gender, age, and social class distribution across groups.

Potential subjects were screened in the following manner. Interested and eligible families were contacted by the project coordinator and asked to respond to a screening questionnaire to confirm the adoptive and diagnostic status of the proband and to obtain information about the other inclusion/exclusion criteria. Families of subjects who met the inclusion/exclusion criteria were asked to participate in the project. The screening and scheduling were conducted by the project coordinator rather than the raters to maintain rater blindness to the referral status of the proband. The study was approved by the institutional review board, and all subjects signed an informed consent (assent for children).

The assessment battery was identical with that used in previous studies of ADHD boys (Biederman et al., 1990, 1992), girls (Biederman et al., 1999), and African-American children (Samuel et al., 1996) in our program. Psychiatric assessment of probands and first-degree relatives used *DSM-III-R*–based instruments. For children and adolescents we used the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic version, 4th edition (K-SADS-E) (Orvaschel and Puig-Antich, 1987), and for adults we used the Structured Interview for *DSM-III-R* (Spitzer et al., 1990), supplemented with modules from the K-SADS-E to cover childhood-onset disorders. Direct interviews were conducted with each parent and with children older than 12 about themselves. In addition, information on all children older than 5 was obtained from the mother or father.

The assessments were conducted by highly supervised clinical raters trained to high levels of interrater reliability. Based on 173 interviews, the mean κ coefficient of agreement between trained raters and a board-certified child and adolescent psychiatrist was 0.8. The raters were blind to the diagnostic as well as the adoptive status of each proband. In addition, the raters did not know which child within the family was the proband until after the entire family had been assessed.

Final diagnostic and the *DSM-III-R* Global Assessment of Functioning score assignment was made after a blind review by a panel of board-certified psychiatrists. Definite diagnoses were assigned to subjects who met all *DSM-III-R* diagnostic criteria. Only definite diagnoses were used to determine the rates of disorders in probands and relatives. Diagnoses presented for review were considered definite only if the committee agreed that criteria were met to a degree that would be clinically meaningful. Diagnoses were made for 2 points in time: lifetime and past month (current). Only lifetime rates of disorder were used in analyses. As in our previous work, the diagnosis of major depression was made only when it was associated with severe impairment to ensure that we were capturing only individuals with clinically significant levels of depression. Similarly, we created a summary category that we termed *multiple anxiety disorders*, defined as having at least 2 anxiety disorders, to capture those individuals with clinically significant levels of anxiety. Use of this category has 2 advantages compared with analyses of individual anxiety disorders. Faraone et al. (1995) showed that it has higher test-retest reliability over a 1-year period. Mennin et al. (2000) used receiver operating characteristic analysis to show that this category correctly identified a large number of ADHD children as anxious while maintaining a reasonable false-positive rate. Socioeconomic status (SES) was evaluated with the Four Factor Index of Social Status (Hollingshead, 1975). This index examines the educational and occupational levels of parents and assigns each family to a socioeconomic level that ranges from 1 (highest) to 5 (lowest).

The data derived from the adoptive first-degree relatives were compared with data derived from the first-degree biological relatives of the ADHD and control probands. For the diagnostic variables, which were dichotomous, omnibus 3×2 χ^2 analyses were conducted. When the omnibus test was significant, it was followed by 2×2 χ^2 tests. As the siblings of probands were not statistically independent of each other because of shared genetic factors, it was necessary to statistically correct for this in the sibling analyses. This was done by using logistic regression with Huber standard errors.

Analysis of variance was used to obtain an overall *F* test when looking at continuous dependent variables. If the overall *F* test was significant, it was followed by pairwise *t* tests. If there was a statistically significant difference among the 3 groups on any of the demographic information (proband age, SES, or family intactness) it was statistically controlled for in the analyses. This was done by using logistic regression. All tests were 2-tailed, and results were considered significant if the *p* value was less than .05.

RESULTS

The demographic characteristics of the 3 groups of probands can be seen in Table 1. There were no significant differences in the mean age, mean SES of the family, percentage of intact families, or percentage of females in each group. As noted above, because only siblings who were full biological children of the adoptive parents were included in these analyses, the number of siblings of adopted probands was quite small. Thus we analyzed the data for parents and siblings separately.

As depicted in Figure 1, no meaningful differences were identified in the rate of ADHD in parents and siblings of adopted children compared with parents and siblings of control probands. In contrast, ADHD was clearly familial in biological parents and siblings of biological ADHD probands (Fig. 1).

In addition, we found that the parents of the biological ADHD probands had significantly higher rates of severe major depression, overanxious disorder, and generalized anxiety disorder when compared with the parents of the other 2 groups of probands (Fig. 2). The parents of the biological ADHD probands had a significantly higher rate of multiple anxiety disorders than did the parents of the control probands. Although the rate of multiple anxiety disorders in the parents of the adopted ADHD probands was lower than the rate in the parents of the nonadopted ADHD probands (14% versus 22%), this difference did not achieve statistical significance. Parents of the adopted ADHD children had a significantly higher rate of stuttering than did the parents of the biological ADHD and control probands.

TABLE 1
Proband Demographics

	Adopted ADHD (*n* = 25)	Biological ADHD (*n* = 101)	Controls (*n* = 50)
Age, yr: mean (SD)	11.4 (4.2)	10.6 (3.2)	10.9 (3.6)
SES[a]: mean (SD)	1.5 (0.5)	1.9 (1.0)	1.9 (0.9)
No. (%) intact	23 (92)	70 (69)	37 (74)
No. (%) females	6 (24)	24 (24)	12 (24)

Note: All results were nonsignificant. ADHD = attention-deficit hyperactivity disorder; SES = socioeconomic status.
[a] Hollingshead (1975).

Although the number of adoptive siblings was quite small, very few disorders were found in this group. With the exception of 1 child with ADHD, 1 child with encopresis, and 2 children with language disorder, no disorders were found in the adoptive siblings. This is in contrast to the siblings of the biological ADHD probands, who displayed high rates of ADHD (31%), severe major depression (13%), oppositional disorder (22%), and multiple anxiety disorders (17%) as well as other associated disorders. Consistent with this finding, the mean Global Assessment of Functioning scores of the parents and siblings of adopted ADHD and control probands were less impaired than those of parents and siblings of the biological ADHD probands (Fig. 2).

DISCUSSION

In a family study of adopted children with ADHD, we found that the rate of ADHD in adoptive parents of

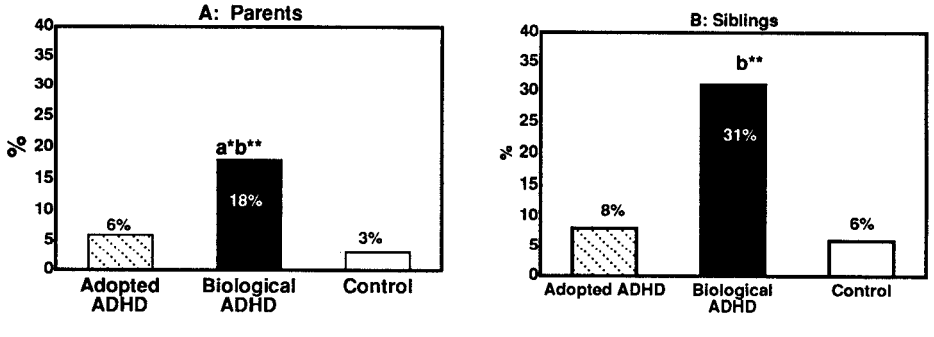

Fig. 1 Rates of attention-deficit hyperactivity disorder (ADHD) in relatives. [a]Versus adopted ADHD; [b]versus control. $^{*}p < .05$; $^{**}p < .01$.

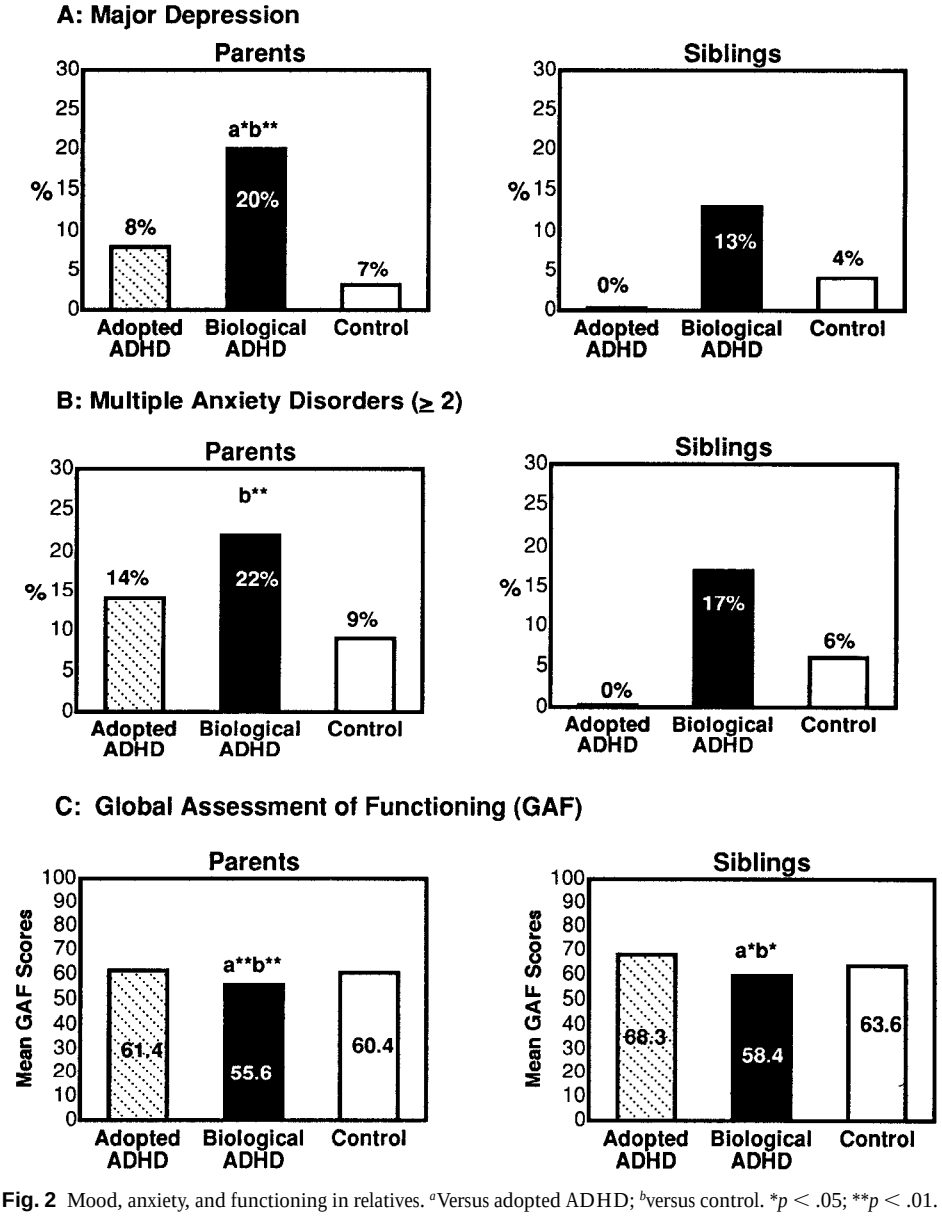

Fig. 2 Mood, anxiety, and functioning in relatives. [a]Versus adopted ADHD; [b]versus control. *$p < .05$; **$p < .01$. ADHD = attention-deficit hyperactivity disorder.

adoptees with ADHD was low and indistinguishable from the rate found in parents of non-ADHD controls and that both were significantly lower than the rate of ADHD in parents of the biological ADHD children. These results confirm our study hypothesis and indicate that there is no increased risk for ADHD among adoptive parents of adopted ADHD probands.

Our findings pertaining to the absence of familial aggregation of ADHD in relatives of adoptees with ADHD are consistent with those of earlier adoption studies. Both Morrison and Stewart (1973) and Cantwell (1975) found higher rates of hyperactivity in the biological relatives of hyperactive probands than in the adoptive relatives of hyperactive probands or biological relatives of control probands. The failure to find evidence for familiality among parents of ADHD adoptees is consistent with mounting evidence supporting a genetic hypothesis for ADHD.

Notably, we found high rates of mood and anxiety disorders among the biological but not the adoptive parents of ADHD probands. This finding is consistent with results of prior family studies of ADHD (Faraone and

Biederman, 1998). Thus our finding provides further support for the idea that these other psychiatric disorders in ADHD families are variable manifestations of the genes that influence ADHD. The fact that adoptive parents of ADHD probands are not at risk for these disorders argues against the idea that these parental disorders are caused by the stress of raising a child who has ADHD.

Our conclusions should be viewed in light of the finding that adoptees are overrepresented among children with *DSM-III* ADD (Deutsch et al., 1982). Although the reasons for this remain unknown, it is likely that the biological parents of the adoptees displayed many of the same impulsive characteristics as their offspring, which may have led to unplanned pregnancies. Support for this hypothesis can be derived from the work of Kessler et al. (1997), who found an association between early-onset psychiatric disorders and teenage pregnancy. Because these risk factors are also associated with risk for early cigarette smoking (Milberger et al., 1997), and because maternal smoking during pregnancy has been found to be a risk factor for ADHD in offspring (Milberger et al., 1996), it is possible that the offspring of these individuals are at extremely high risk for ADHD. More work is needed to investigate the relationships among these variables.

Limitations

The findings in this report should be viewed in light of some methodological limitations. Although statistical significance could be established on the main variables of interest, the small sample size greatly limited our statistical power, raising the possibility of a type II error. Although we had access to a large number of adoptees, only a minority of available subjects had been adopted at birth or shortly thereafter as we required for inclusion in this study. Such a decision to exclude adopted children who were placed with their adoptive family when they were older than 1 year and adopted children who were adopted by a family of a different cultural background were important to avoid introducing other confounding factors that may have clouded interpretation of the findings.

Also, we excluded from the present analyses siblings of adopted ADHD probands who were not biological children of the adoptive parents. Thus, while the data obtained on the siblings of the probands were interesting, there were few statistically significant findings. Perhaps if we had had a much larger sample, there would have been enough siblings to form a large enough group that meaningful conclusions could have been drawn.

Although the rates of disorder and cognitive and psychosocial dysfunction were quite low in the adoptive parents and siblings of the adopted ADHD probands, it would have been interesting to include a group of adopted non-ADHD probands for comparison. An additional problem with the current investigation, and with adoption studies in general, was that data could not be obtained on both the biological and adoptive relatives of the same group of children. However, this type of study is nearly impossible to conduct in the United States because of laws protecting the privacy of individuals who give their children up for adoption. A related problem was that we were unable to obtain information regarding gestational nutrition, prenatal exposure to alcohol and other toxins, or prenatal infections. As it is possible that the adopted probands were exposed to higher rates of prenatal insults, caution must be used in interpreting our data. Nonetheless, the finding that ADHD did not occur more frequently in relatives of the adopted ADHD probands is consistent with the genetic hypothesis of this disorder.

Another potential problem is that we obtained diagnostic information regarding ADHD and other disorders retrospectively from parents. Such an approach to diagnosing ADHD has been validated by our group in multiple research studies examining treatment response (Spencer et al., 1995, 1998), comorbidity (Biederman et al., 1993), neuropsychology (Seidman et al., 1998), and neuroimaging (Bush et al., 1999).

Summary and Clinical Implications

Despite these considerations, we observed that the rates of ADHD and associated disorders were similar in the adoptive relatives of adopted ADHD probands and the biological relatives of non-ADHD control probands and lower than those observed in the relatives of the biological ADHD probands. These findings add to mounting evidence from multiple lines of research strongly supporting a genetic hypothesis for ADHD.

These results are important to clinicians who are providing support for adoptive parents of ADHD children. They should emphasize that environmental factors were not likely the cause of the adoptive child's problems. Moreover, the low rates of psychopathology observed in the adoptive parents suggest that adoptive parents of

ADHD children may be able to follow through on behavioral techniques useful in the treatment of ADHD.

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