Original Article

INFLUENCE OF GENDER ON FAMILIAL AGGREGATION OF ADHD IN RELATIVES OF PROBANDS WITH ADHD

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ABSTRACT

Objective: To assess the influence of gender on familial transmission of ADHD.

Methodology: Two hundred seventy seven probands with ADHD (aged 5-17 years) were screened with clinical interview and the schedule for affective disorders and schizophrenia for School – Age Children Present and Lifetime version (K – SADS – PL). Nine hundred ninty seven first degree relatives (554 parents, 443 siblings) were assessed with interview and K-SADS (for under 18 years) and Wender (for age up to 18 years) for ADHD.

Results: Our findings showed no gender differences in the prevalence of ADHD in relatives of ADHD girls and boys. (prevalence of ADHD Like the boys' families).

Conclusion: The results suggest that boys and girls do not differ in the familial risk factors which contribute in ADHD and the familial aggregation of ADHD in relatives of probands with ADHD. Although this finding is consistent with prior works which suggest more similarities than differences in the nature of ADHD in boys and girls, they are not conclusive and more controlled studies are needed.

KEYWORDS: ADHD, Gender differences, Genetics.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous disorder estimated to effect 6-9% of school age children.[1,2] In family studies of ADHD, relatives of ADHD children were found to be at high risk for the disorder,[3] twin and siblings studies suggest that genes mediate this familial aggregation.[3-8] One potential indicator of genetic heterogeneity in ADHD is high level of comorbidity with conduct, mood and antisocial disorders.[1,3] Gender differences may also provide clues to the genetic heterogeneity of ADHD.[1]

In clinics, the male – female ratio is about 9 to 1; in the community, it is 4 to 1.[9] Indeed, any etiological model of ADHD must explain why the disorder is two to nine times more prevalent among boys compared with girls.[3] Family studies provide a convenient tool for determining whether gender differences in population prevalence indicate gender differences in familial etiological factors.[3]

In the "familial dose" model, this difference is accounted for by the assumption that girls, in comparison with boys, need more familial risk factors to develop ADHD.[3,4,10,11] Because it is assumed that ADHD girls carry a higher dose of familial risk factors, than their relatives should also carry more and thus be at greater risk for ADHD than are the relatives of ADHD boys.[4] For example, if ADHD is a single gene disorder, then perhaps females require two copies of the pathogenic gene whereas males only require one. Because the probability of

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having two genes is lower than the probability of having, at least one ADHD would be less prevalent among females. However, because ADHD mothers always have two copies of the gene, then the probability of transmitting one to their off spring is 100%. This is clearly greater than the probability of an ADHD fathers transmitting a pathogenic gene. Thus, the greater genetic loading of ADHD mothers, compared with ADHD fathers, confers a greater risk to their children. Family studies can evaluate the familial dose model of gender effects because it predicts that the relatives of female ADHD probands will be at greater risk for ADHD than the relatives of male ADHD probands. However, among relatives, females should always be at lower risk for ADHD compared with male.[3] Two studies have found more psychopathology among relatives of ADHD girls compared with relatives of ADHD boys.[3,4,11,12]

In six studies, however, researchers did not find a greater risk for psychopathology among relatives of girl ADHD probands.[4,13-15] These conflicting results could reflect the hypothesized genetic heterogeneity of ADHD. The present report focuses on the families of probands with ADHD. We predicted that the relatives of ADHD girls would be at higher risk for ADHD than would relatives of ADHD boys.

PATIENTS AND METHODS

Subjects: We studied two groups of probands with ADHD wherein One hundred thirty six girls with ADHD were compared with 141 boys with ADHD. These groups had 997 first-degree biological relatives, who provided data. All probands were between the ages of 6 and 18 years. All of the ADHD probands met the full DSM-V diagnostic criteria for ADHD at the time of the clinical referral; at the time of recruitment they all had active symptoms of the disorder. All subjects older than 12 gave written informed consent for participation. Parents gave written informed consent for participation of children under 12 and these children participated only if they assented to the study procedures.

Potential subjects were excluded if they had been adopted, or if their nuclear family was not available for study. We excluded subjects if they had major sensorimotor handicaps (paralysis, deafness, blindness), psychosis, autism, or a Full-Scale IQ less than 80.[16]

We selected psychiatrically referred ADHD probands from consecutive referrals to a child and adolescent psychiatry clinic at the Sheikh Hospital clinic (a subspecial hospital for children in Mashhad, Iran) Subjects were enrolled in the study between November 2002 and March 2004. Parents, pediatricians and schools had referred these children for psychiatric evaluations.

Procedure: We used DSM-IV-based structured interviews for diagnoses of ADHD. The psychiatric assessments of the probands and siblings under 18 relied on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (K-SADS-E).[17] Diagnoses were based on independent interviews with the mothers and direct interviews with the probands and their siblings. Children younger than 12 years of age were not interviewed directly. Each parent and sibling over 18 were interviewed directly and we used DSM-IV-based structured interviews and the Wender Utah Rating scale for the best estimate diagnoses of ADHD.[18]

The interviewers were blind to proband diagnosis. The direct interviews of the mothers and the direct interviews of the children were conducted by different raters. For about 90% of the families, the mother was interviewed about their children. The raters were trained and supervised by board-certified psychiatrists. The psychiatrists making the diagnoses were board certified in both child and adult psychiatry and were blind to all data collected from family members.

Statistical Analyses: Chi-square tests were used to compare risk of ADHD in the relatives of ADHD probands between girls & boys groups. Pvalue >0.05 were considered not significant.

RESULTS

The study enrolled 141(50.9%) male and 136(49.1%) female. Most of the study subjects 185(66.8%) were between 7-12 years of age. We didn't find greater risk of ADHD mothers

Table-I: Prevalence of ADHD in siblings of Female and Male subjects with Attention Deficit Hyperactivity Disorder (ADHD)a

ADHD in Parents	*Male Subjects(%)*	*Female Subjects(%)*	*Statistic*	*OR/(95% CI)*
no	71(50.4)	66(48.5)		
One parent	26 (52)	58(42.6)	X^2=1.620;Pv=0.445	
Both parents	9(18)	12(8.8)		
Father	37(63)	70(51.5)	X^2=1.27;Pv=0.258	1.313(0.819-2.106)
Mother	18(12.8)	27(19.9)	X^2=2.555;Pv=0.110	1.693(0.844 -3.242)
ADHD in siblings	*Male Subjects(%)*	*Female Subjects(%)*	*Statistic*	*OR/(95% CI)*
No	102(72.3)	116(85.3)	X^2=6.9;Pv=0.02	1.57(1.076-2.290)
Have	39(27.7)	20(14.7)		

compared with ADHD fathers. We also failed to identify any statistically significant differences in genetic loading in comparisons of boys and girls with ADHD. If one or both parents were affected, the rate of ADHD among the girls isn't different with boys.

The rate of ADHD among the siblings of the ADHD girls (14.7%, N=20) is as the same as among the siblings of the ADHD boys (27.7%, N=39) (x^2=6.9, df=1, p>0.01;) (Table-I). We didn't find significant differences in the prevalence of ADHD among the first relatives of ADHD boys and girls (60.3%, N=85) (58.1%, N=57) (x^2=0.138, df=1, p>0.01;) (Table-II).

DISCUSSION

Understanding the genetic etiology of ADHD could significantly improve our diagnosis, early detection and the development of better interventions in the treatment of this condition. The rate of ADHD among the relatives of the ADHD girls is the same as among the relatives of the ADHD boys. These findings refute our hypothesis, the prediction that relatives of girl probands would have higher rates of ADHD than relatives of boy probands. This finding is consistent with other studies.[4,13-15] Thus, the different prevalences of ADHD between boys and girls cannot be attributed to any familial transmission model that propose that, compared with boys, girls require a greater "dose" of familial risk factors to express ADHD.

If, as our data suggest, the genetic contributions to ADHD are similar in boys and girls, this may indicate similarities in other biological features. Consistent with this idea are the findings of Sharp et al.[20] They found that, in addition to showing similarities in a wide range of clinical features, ADHD girls and boys did not differ in their clinical response to either methylphenidate or dextroamphetamine. In contrast, other studies suggest biological differences between ADHD boys and girls, data reported earlier[21] suggest that girls with ADHD may not have executive deficits, may be less vulnerable to such deficits, or may have a form of executive function deficits that differs from that for boys. On the other hand, a neuroimaging study by Ernst et al[22] suggested significant brain dysfunction for ADHD girls but not boys. Clearly, more work is needed to determine if gender differences exist in the biological underpinnings of ADHD. Our results must be interpreted in the context of methodological limitations. Because our sample was referred by psychiatrists and paediatricians we do not know to what degree these findings will generalize to ADHD children in the community.

In addition, although raters were blind to the diagnosis of probands, parents were not. It is possible that parents of ADHD children might have been more likely to recall similar problems in their own childhood. This may have

Table-II: Prevalence of ADHD in relatives of female and male subjects with Attention Deficit Hyperactivity Disorder (ADHD)a

ADHD in siblings	*Male Subjects(%)*	*Female Subjects(%)*	*Statistic*	*OR/(95% CI)*
No	56(39.7)	57(41.9)	X^2=0.138;Pv=0.710	0.913(0.565-1.475)
Have	85(60.3)	79(58.1)		

been exacerbated when the probands were actively symptomatic. Another potential source of bias stems from the lack of direct interviews with children younger than.[12] This method for assessment of psychopathology in the children may have led to under-representation of psychopathology in this group. Notably, these methodological limitations apply equally to our boy and girl proband families. This suggests that they did not confound gender comparisons or our assessment of proband gender by proband diagnosis interactions.

Despite these limitations, our results show similar patterns in the familial transmission of ADHD in families of ADHD boys and girls. Thus, although ADHD is associated with the familial transmission of ADHD, the pattern of transmission is not influenced by the proband's gender. These similar patterns provide further evidence for the idea that, when ADHD is diagnosed in girls, it corresponds to the same disorder diagnosed in boys. Our data support the idea that gender and ADHD are independent risk factors for the familial transmission of ADHD. The higher risk for attention deficit disorder could not be accounted for by gender or generation of relative.

Our results suggest that boys and girls do not differ in the familial risk factors that mediate ADHD and the familial aggregation of ADHD in relatives of probands with ADHD. Although this is consistent with prior work suggesting more similarities than differences in the nature of ADHD boys and girls, we cannot make strong conclusions, thus replication studies and further work is needed to better understand these features of ADHD and their implications for understanding the etiology of the disorder.

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