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DOES EXPOSURE TO MATERNAL SMOKING DURING PREGNANCY AFFECT THE CLINICAL FEATURES OF ADHD? RESULTS FROM A CONTROLLED STUDY

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Abstract

Objectives—Exposure to maternal smoking during pregnancy may be a significant risk factor for attention-deficit/hyperactivity disorder (ADHD) independently of family history of ADHD. The main aim of this study was to examine whether the clinical profile of ADHD differs between children with and without exposure to maternal smoking during pregnancy.

Methods—This was a case-control study of boys and girls with and without ADHD ascertained from psychiatric and pediatric sources. Maternal smoking during pregnancy was defined by interviews with subjects' mothers. Main outcome measures were ADHD symptoms and associated clinical features in children with and without exposure to maternal smoking during pregnancy.

Results—No significant differences were found between ADHD children with and without exposure to maternal smoking during pregnancy on clinical characteristics. When these analyses were repeated in the subgroup of subjects without parental history of ADHD, there were also no statistically significant differences found.

Conclusions—Despite adequate statistical power, no significant differences were found between ADHD children with and without exposure in the clinical features of ADHD and associated disorders. Results provide support for the notion that ADHD cases resulting from

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exposure to maternal smoking during pregnancy have similar clinical profiles as other ADHD cases.

Keywords

ADHD; smoking; children; brain development; childhood ADHD

INTRODUCTION

Several studies have suggested that maternal smoking during pregnancy is a risk factor for ADHD in offspring (Banerjee et al. 2007; Langley et al. 2005; Linnet et al. 2003; Milberger et al. 1996; Milberger et al. 1998). For example, we found that ADHD children were significantly more likely to have been exposed to cigarettes in utero than were controls, even after adjusting for several other risk factors (Mick et al. 2002). Landgren et al. (1998) reported that maternal smoking increased the risk for deficits in attention, motor control, and perception (DAMP), a syndrome that overlaps with ADHD considerably. Other studies concluded that maternal smoking might not cause ADHD. For example, by examining offspring conceived with assisted reproductive technologies, Thapar et al. (2009) compared the effects of maternal smoking on offspring who were and were not genetically related to the mother. They found effects of maternal smoking on ADHD, but these effects were greater for genetically related offspring suggesting that an inherited effect contributes to the observed association in other studies.

Although the mechanisms by which exposure to nicotine during pregnancy increases the risk for the development of ADHD have not been elucidated, several possible explanations have been advanced. Studies suggest that nicotine affects the serotonin and dopaminergic systems, brain cell growth, and DNA and RNA synthesis of the developing brain of the fetus (Wakschlag et al. 1997). Roy et al. (1998) found increased incidence of apoptotic cells in the hindbrain, forebrain, and midbrain of rat embryos exposed to nicotine, and reported that damage to the developing neuroepithelium was evident at levels of prenatal exposure to nicotine that were insufficient to cause general dysmorphogenesis. Thus, nicotine exposure may result in the disruption of normal brain development that could lead to behavioral and attentional problems leading to the constellation of clinical symptoms known as ADHD. However, whether the clinical features of ADHD resulting from maternal smoking during pregnancy are distinguishable from those resulting from other etiological mechanisms remain unknown.

The main aim of this study was to evaluate whether exposure to maternal smoking during pregnancy is associated with a unique clinical phenotype. Should such a phenotype be available, it could help explain some of the discrepant findings in the literature. To this end, we compared the clinical features of children with ADHD who were exposed to maternal smoking during pregnancy against children with ADHD who were not exposed.

METHODS

Detailed study methodology has been previously described (Biederman et al. 1992; Biederman et al. 1999). Briefly, subjects were derived from two identically designed, longitudinal case-control family studies conducted at the Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD at Massachusetts General Hospital. These studies ascertained families on the basis of a case (ADHD) or control (non-ADHD) proband child aged 6-17 years at time of ascertainment. These studies were comprised of 140 ADHD and 120 non-ADHD control boys and 140 ADHD and 122 non-ADHD control girls. A total

of 262 subjects with ADHD were available for this analysis (the non-ADHD controls were not used for this analysis).

For both studies, potential probands were excluded if they had been adopted, if their nuclear families were not available, if they had major sensorimotor handicaps (paralysis, deafness, blindness), if they had psychosis or autism, or if they were unable to participate in the assessments due to language barriers or an estimated IQ <80. After a complete description of the study, parents provided written informed consent for their children, and children and adolescents provided written assent. The Institutional Review Board at Massachusetts General Hospital approved this study.

Psychiatric assessments relied on the K-SADS-E (Epidemiologic Version) (Orvaschel 1994) for subjects less than 18 years of age and the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al. 1992) (supplemented with modules from the K-SADS-E to assess childhood diagnoses) for subjects aged 18 and older. Diagnoses were based on direct interviews with the mothers and the offspring, except for children <12 years that were not interviewed directly. Both lifetime and current (i.e., in the past month) diagnoses were collected. Lifetime (in the past when things were at their worst) and current impairment in daily functioning associated with ADHD was coded as mild, moderate, or severe. We combined data from direct and indirect interviews by considering a diagnosis positive if it was endorsed in either interview. All interviews conducted were blind to the subject's referral source. Diagnoses were considered positive if DSM-III-R criteria were unequivocally met. A committee of board-certified child and adult psychiatrists, who were blind to the subject's ascertainment status and all other data, resolved diagnostic uncertainties. Diagnoses presented for review were considered positive only if a consensus was achieved that criteria were met to a degree that would be considered clinically meaningful.

All interviewers had undergraduate degrees in psychology and were trained to high levels of inter-rater reliability. First, they underwent several weeks of classroom style training, learning interview mechanics, diagnostic criteria, and coding algorithms. Then, they observed experienced raters and clinicians conduct interviews. They subsequently conducted at least six practice (non-study) interviews and at least two study interviews while being observed by senior interviewers. We computed kappa coefficients of agreement by having child and adult psychiatrists and clinical psychologists diagnose subjects from audio taped interviews. Based on 500 assessments from interviews of children and adults, kappa coefficient for ADHD was 0.88. Socio-economic status (SES) was assessed with the 5-point Hollingshead scale (Hollingshead 1975), using the occupational and educational status of the parents.

Measurement of Exposure to Maternal Smoking During Pregnancy

Maternal smoking during pregnancy was coded positive if the mother answered "yes" to the following question during the indirect structured interview: "Did you smoke as much as a pack a day for at least 3 months while pregnant with this child?" Maternal smoking during pregnancy was also coded positive if during the direct structured interview the mother met criteria for nicotine abuse or dependence during the time she was pregnant with the child (utilizing the reported onset and offset of nicotine abuse/dependence and the date-of-birth of the child). Nicotine abuse cases were defined as the endorsement of smoking any amount of cigarettes four to six days per week. We included abuse cases to capture regular smoking habits that, while not as serious as dependence, still represent a potential risk to the fetus. This second definition was only used in the Girls ADHD study, as the Boys ADHD study did not assess nicotine abuse/dependence in the mothers' structured interview. The data

needed to create this variable was available for all but one subject, leaving a sample size of 261.

Statistical Analysis

First, we examined demographic characteristics in subjects with ADHD, stratified by exposure status, using Chi Square tests and one-way analysis of variance for categorical and dimensional variables, respectively. Variables that were associated with exposure at the $p < 0.05$ level were added as covariates in our analyses. Second, we compared subjects with and without exposure to maternal smoking during pregnancy on the lifetime prevalence of each ADHD symptom, ADHD subtype (i.e., inattentive versus hyperactive/impulsive), age of ADHD onset, and persistent ADHD. Persistent ADHD was defined as current (last month) full or subthreshold ADHD at the 10-year (boys) (Biederman et al. 2006) or 11-year (girls) follow-up assessment (Biederman et al. 2010). For the analysis of symptoms and subtype status, we estimated negative binomial and logistic regression models, respectively, with the clinical outcome as the dependent variable and exposure status and any covariates as the independent variables. For the analysis of age of ADHD onset, we estimated a negative binomial regression model with the clinical outcome as the dependent variable and exposure status and any covariates as the independent variables. All tests were two-tailed, and alpha was set at 0.05.

RESULTS

Demographic Characteristics

As shown in table 1, there were no meaningful differences between the groups (Not Exposed: $n=191$; Exposed: $n=70$) on sex, parental ADHD, age, or lifetime history of medication use for ADHD. However, the exposed group was significantly more likely to have had prenatal exposure to other substances (e.g., alcohol). Also, significant differences were found in mothers' mean age at offspring birth and family social class, with the exposed group having mothers with a lower mean age and families with a less affluent social class. Consequently, all subsequent analyses were adjusted for maternal use of alcohol or drugs during pregnancy, mothers' age at offspring birth and family social class.

Next, we compared children with ADHD with and without exposure to maternal smoking during pregnancy on the clinical features of ADHD. We found no significant differences between the groups on the rates of any of the fourteen DSM-III-R ADHD symptoms, (all p -values > 0.05 , odds ratios between 0.6 and 2.8). Also, there was no association between exposure status and ADHD subtype (inattentive: $p=0.50$, odds ratio=1.3; hyperactive-impulsive: $p=0.98$, odds ratio=1.0), parental ADHD ($p=0.28$, odds ratio=1.4), age of ADHD onset ($p=0.29$, $\beta=0.1$), ADHD impairment ($p=0.89$, odds ratio=1.0), or ADHD persistence ($p=0.98$, odds ratio=1.0) after adjustment for social class, maternal age at birth and exposure to other substances. When these analyses were repeated in the subgroup of subjects without a parental history of ADHD (Not Exposed group: $n=129$; Exposed group: $n=40$), again no statistically significant differences were found (all p values > 0.05 , odds ratios between 0.4 and 3.1).

DISCUSSION

In a large sample of psychiatrically and pediatrically ascertained youth with and without ADHD of both sexes, we found no evidence for an association between prenatal exposure to maternal smoking during pregnancy and the clinical features of ADHD. These results were maintained within the stratum of subjects without a family history of ADHD. These results

support the notion that ADHD cases that may have resulted from prenatal exposure to nicotine are clinically indistinguishable from ADHD cases without such exposure.

Children with ADHD with and without exposure to maternal smoking during pregnancy had indistinguishable rates of the fourteen DSM-III-R ADHD symptoms. This is particularly noteworthy considering that children with ADHD exposed to maternal smoking during pregnancy could have met criteria for ADHD with a very different set of ADHD symptoms than other ADHD children without such exposure. Likewise, there was no association between exposure status and ADHD subtype (i.e., inattentive, hyperactive-impulsive, combined), parental ADHD, age of ADHD onset or ADHD impairment, after adjustment for social class, maternal age at birth and exposure to other substances.

Thus, to the extent that the profile of clinical features corresponds with underlying neuropathophysiology, these findings support the hypothesis that exposure to maternal smoking during pregnancy results in the same neurobiological abnormalities that underlie other cases in which ADHD originated from familial and other non-familial risk factors. This hypothesis is further supported by the observation of phenotypic similarities in the clinical picture of ADHD observed in the subgroup of ADHD children exposed to maternal smoking during pregnancy without a parental history of ADHD. This finding suggests that the effects of nicotine on the fetal brain may be biologically consistent with current neurobiological models of ADHD as a brain disorder resulting from structural abnormalities in cortico-cortical and fronto-subcortical pathways (Biederman 2005; Nigg et al. 2005; Sonuga-Barke 2005)

They also suggest that similar neurobiological underpinning may be operant in ADHD stemming from genetic and environmental etiological risk factors. These intriguing results would suggest that nicotine exposure during pregnancy could represent an ecologically valid and informative animal model for ADHD.

Our findings are consistent with those of Ball et al. (2010), who found no differences in age of onset, number of symptoms, or likelihood of remission between ADHD subjects with and without a history of maternal smoking during pregnancy. However, Ball et al. (2010) also found no association between maternal smoking during pregnancy and the risk for ADHD in offspring. Further studies should try to reconcile the discrepant findings in the literature.

Our results should be considered in the light of methodological limitations. Because our sampling consisted largely of Caucasian subjects, our results may not generalize to other racial or ethnic groups. Because the children were clinically referred, our results may not generalize to community samples. They do, however, generalize to pediatric and psychiatric samples. Because our data were originally collected prior to the publication of DSM-IV, we were only able to examine DSM-III-R symptoms. However, there is a very high overlap between the two definitions (93% of DSM-III-R cases received a DSM-IV diagnosis) (Biederman et al. 1997). Future studies should seek to replicate these findings using DSM-IV criteria. Parents' ADHD diagnoses were made using the K-SADS, which is validated only for children. Use of an adult ADHD scale may yield different results. Our measure of maternal smoking during pregnancy was based on retrospective reports from the mothers (after 6 to 17 years, depending on the age of the child at the time of interview), and may be subject to recall bias. We attempted to deal with this bias by including information from both direct questioning regarding substance use during pregnancy as well as a separate interview of the mother in which it was not known (to the subject or interviewer) that we would later use information collected regarding her history of smoking to recalculate in utero exposure to her children. Also, our measure was binary, and we were unable to test the effect of varying magnitudes of exposure on offspring outcomes. Future studies would

benefit from longitudinal study designs and more detailed measures of maternal smoking. Although we controlled for exposure to other drugs in our results, future studies should strive for samples with only smoking exposure and no other confounding drug exposures. Although not reaching statistical significance, the rate of parental ADHD was somewhat higher in the exposed group versus the not exposed group (43% versus 32%). Future studies should examine this relationship to verify that our result was not a type I error. Also, our analysis was based on the assumption that the etiological pathway of exposed cases included the exposure. It is possible that among exposed cases, the exposure was not a factor in the pathogenesis of the disease.

Despite these limitations, our results indicate that children with ADHD who had prenatal exposure to maternal smoking are indistinguishable from children with ADHD without such exposure on clinical correlates of ADHD. These results support the notion that ADHD cases resulting from exposure to maternal smoking during pregnancy have similar neurobiological brain abnormalities as other ADHD cases.

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Table 1

Demographic characteristics of children with ADHD with and without prenatal exposure to maternal smoking

Demographic Characteristic	Not Exposed n=191	Exposed n=70	Test Statistic, p value
Sex (male)	108 (57)	31 (44)	$\chi^2_{(1)} = 3.1, p=0.079$
Exposure to other drugs ¹	17 (9)	14 (20)	$\chi^2_{(1)} = 5.9, p=0.015$
Parental ADHD	62 (32)	30 (43)	$\chi^2_{(1)} = 2.4, p=0.119$
Maternal Age at Birth	29.5±4.9	27.5±4.6	t (259) = 3.0, p=0.003
Offspring Age	10.8±3.3	11.2±2.8	t (259) = -0.8, p=0.397
Social Class ²	1.7±0.9	2.3±1.1	t (259) = -4.0, p<0.001
Lifetime history of medication for ADHD	147 (77)	54 (77)	$\chi^2_{(1)} = 0.0009, p=0.976$

Values in table represent *mean±standard deviation* or *frequency (percent)*¹Prenatal exposure to alcohol and/or illicit substances²Measured by the Hollingshead scale; values range from 1 (most affluent) to 5 (least affluent)