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RESEARCH ARTICLE

Increased Risk of Asthma in Children with ADHD: Role of Prematurity and Maternal Stress during Pregnancy

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Abstract

Objective: ADHD and asthma are prevalent conditions in childhood, with complex pathophysiology involving genetic-environmental interplay. The study objective is to examine the prevalence of asthma in our ADHD population and explore factors that may increase the risk of developing asthma in children with ADHD. **Methods:** We retrospectively analyzed the presence of maternal stress during pregnancy and history of asthma in 201 children diagnosed with ADHD. **Results:** Chi-square analysis indicated significant higher presence of asthma in our ADHD sample compared to Quebec children, $\chi^2(1, N = 201) = 15.37$, $P<0.001$. Only prematurity and stress during pregnancy significantly predicted asthma in a logistic regression model, $\chi^2(2)=23.70$, $P<0.001$, with odds ratios of 10.6 (95% CI: 2.8-39.5) and 3.2 (95% CI: 1.4-7.3), respectively. **Conclusion:** Children with ADHD have a higher prevalence of asthma than the general Quebec pediatric population. Children with ADHD born prematurely and/or those whose mothers experienced stress during pregnancy have a significantly increased risk of developing asthma. The study highlights the importance of potentially offering social and psychological support to mothers who experienced stress during pregnancy and/or are at risk of delivering prematurely.

Key Words: *maternal stress during pregnancy, ADHD, asthma, childhood*

Résumé

Objectif: Le TDAH et l'asthme sont des affections prévalentes dans l'enfance, avec une pathophysiologie complexe impliquant une interaction génétique-environnementale. L'étude vise à examiner la prévalence de l'asthme dans notre population TDAH et à explorer les facteurs qui peuvent accroître le risque de développer l'asthme chez les enfants souffrant du TDAH. **Méthodes:** Nous avons analysé rétrospectivement la présence de stress maternel durant la grossesse et les antécédents d'asthme chez 201 enfants ayant reçu un diagnostic de TDAH. **Résultats:** L'analyse du chi-carré a indiqué la présence significativement plus élevée d'asthme dans notre échantillon TDAH comparativement aux enfants du Québec, χ^2 (1, N = 201) = 15,37; P<0,001. Seuls la prématurité et le stress maternel durant la grossesse prédisaient significativement l'asthme dans un modèle de régression logistique, $\chi^2(2) = 23,70$; P<0,001, avec des rapports de cotes de 10,6 (IC à 95% 2,8 à 39,5) et de 3,2 (IC à 95% 1,4 à 7,3), respectivement. **Conclusion:** Les enfants souffrant du TDAH ont une prévalence d'asthme plus élevée que la population pédiatrique générale du Québec. Les enfants souffrant du TDAH nés prématurément et/ou ceux dont les mères ont éprouvé du stress durant la grossesse ont un risque significativement accru de développer l'asthme. L'étude souligne l'importance d'offrir potentiellement un soutien psychologique et social aux mères qui éprouvent du stress durant la grossesse et/ou sont à risque d'accoucher prématurément.

Mots clés: *stress maternel durant la grossesse, TDAH, asthme, enfance*

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD), one of the most common behavioral disorders in children, is a constellation of persistent inattentive and/or hyperactive-impulsive symptoms leading to significantly impaired functioning in social, academic, or occupational spheres (Castle, Aubert, Verbrugge, Khalid, & Epstein, 2007). It has an estimated prevalence of 8-10% in the 4-17 years old (Warikoo & Faraone, 2013).

ADHD has been associated with significant co-morbidities, including other behavioral disorders, and allergic diseases (Cherkasova, Sulla, Dalena, Pondé, & Hechtman, 2013; Chen et al., 2014). Asthma, one of the major allergic diseases, is considered the most common chronic condition in children. It is defined as a chronic inflammatory lung disease characterized by cough, wheezing, dyspnea, and paroxysmal chest tightness in the context of reversible airway narrowing and increased airway responsiveness to a variety of stimuli (National Asthma Education and Prevention Program (NAEPP), 2007).

The respective etiologies of ADHD and asthma are multifactorial, with an intricate interplay of genetic and environmental factors. Through twin and adoption studies, the heritability of ADHD has been estimated to be 76% (Faraone et al., 2005). Previously identified environmental factors include obstetrical complications, smoking, alcohol use and stress during pregnancy, and psychosocial adversity (Grizenko, Shayan, Polotskaia, Ter-Stepanian, & Joober, 2008; Grizenko et al., 2012; Linnet et al., 2003; Langley, Holmans, van den Bree, & Thapar, 2007).

The development of asthma involves a combination of host and environment factors occurring at critical moments in the maturation of the immune system (Sly, 2011). Two of the most important environmental factors in the onset and course of the disease are airborne allergens and viral respiratory infections. Other environmental risk factors have been proposed, such as maternal smoking during pregnancy, household smoking or air pollution (NAEPP, 2007). Various perinatal factors have also been recognized. In a Finnish population-based register study, Metsälä et al. reported that maternal asthma, low gestational age and low ponderal index increased the risk of developing asthma in childhood (2008). In a meta-analysis by Jaakkola et al. (2006), preterm delivery was shown to increase the risk of asthma. A possible explanation is that the lungs of preterm infants are not fully developed both anatomically and immunologically.

Since the 1970s, the prevalence of asthma in industrialized countries has continuously increased (Eder, Ege, & von Mutius, 2006; Anandan, Nurmatov, van Schayck, & Sheikh, 2010). According to Statistics Canada, more than 13% of Canadian children aged 0 to 11 had been diagnosed with asthma by 2000-01, noting a significantly increased prevalence since 1994-95 (11.1% in 1994-95; 13.4% in 2000-01). This trend was also noted in Quebec (11.3% in 1994-95; 15.1% in 2000-01) (Garner & Kohen, 2008). However, the prevalence of asthma among Quebec children has decreased in the last decade (13.2% in 2006-07; 10.6% in 2008-09). Interestingly, this decrease in prevalence of asthma paralleled a concomitant decrease in tobacco smoking, suggesting that the latter has likely contributed to the decreased prevalence of asthma in young children (Thomas, 2010).

Over the years, the controversial 'hygienist theory' has gained acceptance as a possible explanatory model for the worldwide increase in the prevalence of asthma, despite regional variations. This model postulates that there exists an inverse relationship between systemic childhood infections and the subsequent development of atopic disease (Effros & Nagaroj, 2007; Olszak et al., 2012). The decrease in childhood infections is thought to modulate immune deviation processes, ultimately leading to a decreased conversion of T2 helper cells (T_H2) to T1 helper cells (T_H1), while atopic asthma has been associated with a predominant activation of the former (von Hertzen, 2002). In addition to the 'hygienist hypothesis', the role of maternal stress during pregnancy has also been evoked as an important factor impacting on the future onset of asthma, by modulating the developing fetal immune system (Wright, 2008).

The 'excess cortisol' hypothesis was elaborated to offer an explanation of these adverse effects (Edwards, Walker, Benediktsson, & Seckl, 1993). Enzyme 11B-hydroxysteroid dehydrogenase type II (11B-HSD type II) deactivates cortisol in the placenta, thereby limiting the amount of this steroidal hormone in the fetus. Some authors have suggested that 11B-HSD type II becomes saturated under severe maternal stress, leading to increased levels of cortisol in the fetus. Higher maternal levels of cortisol have been associated with a variety of detrimental effects in infancy and later in life (Hamlin, 2012). The release of catecholamines in the context of stressful stimuli, thereby leading to systemic vasoconstriction and consequent decrease in fetal nutrient and oxygen delivery, has been proposed as an alternative theory explaining the fetal adverse effects of prenatal stress.

Results reported by Grizenko et al. demonstrated that children who develop ADHD were exposed to higher levels of maternal stress during pregnancy compared to their non-ADHD siblings (OR = 6.3) (2012). This study validated numerous previous reports suggesting that prenatal stress may have a lasting impact on the child's behavior (Grizenko et al., 2008; Rodriguez & Bohlin, 2005; van den Bergh & Marcoen, 2004). Using an intra-familial design, this study allowed to control for potential family, environment and genetic confounders (Grizenko et al., 2012).

In a systematic review investigating whether atopic disease constitutes a risk factor for ADHD, Schmitt et al. (Schmitt, Buske-Kirschbaum, & Roessner, 2010) examined 20 epidemiologic studies, all suggesting a positive association between atopic diseases and ADHD. For asthma, the

relationship was weak to moderately strong, with ORs below 2.5. One important common feature between ADHD and allergic disorders is the potential impact of prenatal stress on their respective natural history. The adverse effects of maternal stress on the developing fetus are recognized in the literature, notably at the level of neuronal maturation (Harris & Seckl, 2011), fetal lung development (Ward, 1994), and immune system modulation (Wright, 2008).

The objective of this study is to assess whether children with ADHD in our sample present a different prevalence of asthma than children in the general Quebec population and explore what specific factors may increase the risk of asthma in the ADHD population.

Patients and Methods

Sample

Two hundred one children (155 males and 46 females) with ADHD, aged between six and 12 years (mean=9.20; SD=1.0), were consecutively recruited from the ADHD clinic at the Douglas Mental Health University Institute in Montreal (DMHUI), Quebec, Canada. The children were referred to the clinic by their schools, social workers, general practitioners or pediatricians. Upon agreement of the child to participate, signed consent was obtained from the parents.

All children were diagnosed with ADHD following the criteria established in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) by a child psychiatrist on the basis of parental and school reports, an interview with the child and parents, and the Diagnostic Interview Schedule for Children Version IV (DISC-IV). The child's symptoms were evaluated by his parents using the Child Behavioral Checklist (CBCL) and the Conner's Global Index for Parents. Exclusion criteria consisted of an IQ less than 70 on the Weschler Intelligence Scale for Children IV (WISC-IV), a diagnosis of autism, Tourette's disorder, or psychosis.

This study is an exploratory investigation embedded in a larger registered pharmacogenetics study (Clinical trial registry number NCT00483106) started in 1999. Only a subsample of patients were included in the present study, given that questionnaires assessing asthma were only introduced in 2008. Therefore, our sample consisted of children assessed sequentially from 2008.

Assessment

In order to establish the current or past diagnosis of asthma in our study participants, we systematically assessed all participants' past medical history for asthma and other atopic diseases through detailed parental questionnaires. Parents were asked to complete a written report about the medical history of their child. They were asked to explicitly report about previous history of asthma and other atopic disorders. These questionnaires also included information on current or past history of pharmacological prescriptions. Treatments such as beta-adrenergic inhaled bronchodilators and inhaled corticosteroids were used to support a clinical history of asthma. Lastly, participants were evaluated by one staff psychiatrist (NG) regarding atopic disease, while also performing a full review of systems.

Pregnancy, delivery and perinatal complications were systematically assessed using the Kinney Medical Gynaecological Questionnaire and scored using the McNeil-Sjöström scale (Ben Amor et al., 2005). Mothers were asked detailed questions about pregnancy and birth complications. Medical records were available for corroboration in over 80% of cases. The McNeil-Sjöström scale assigns a score of 1 to 6 to each complication, depending on its severity. Mothers who had one or more obstetrical complication scaled 4 or higher were considered as having had significant complications (e.g. c-section, gestational diabetes, prematurity, fetal distress). In the same questionnaire, mothers were asked if they had smoked during their pregnancy and if the child was born prematurely (<37 week gestation).

During the same interview, mothers were asked to describe stressful life events they experienced during their pregnancy. To corroborate and decrease recall bias, medical and obstetrical records were examined and a separate interview was held with a person who was close to the mother at the time of the pregnancy, such as her husband or her own mother, when possible. The information was then used to score maternal stress levels from 1 to 5 based on the DSM-III and DSM-III-R axis IV scales (1 = none, 2 = mild, 3 = moderate, 4 = severe and 5 = extreme). Subjects were divided into two categories: those whose mother had experienced no or mild stress (e.g. arguments with friends) and those whose mother had experienced moderate, severe or extreme stress during pregnancy (e.g. parental separation, repeated physical or sexual abuse, imprisonment of spouse or death of a very close relative).

Statistical analysis

The frequency of past or present asthma in our sample was compared to its prevalence among Quebec children aged 2-7 (10.6%) in 2008-09 (Thomas, 2010) with a chi-square for goodness of fit. Of note, most of our sample was between two and seven in 2008-09. Clinical and demographic characteristics were compared between asthma affected and non-affected children in our sample using Pearson's chi-square for categorical data and Student's t-tests for continuous data. A logistic regression analysis was conducted to determine which factors contributed to the risk of asthma in children with ADHD. Entered into the equation were factors previously associated with asthma in the literature: prematurity, smoking during pregnancy, obstetrical complications, maternal stress during pregnancy, family income, history of breastfeeding, gender and age. The

Table 1. Demographic and clinical characteristics of children with or without asthma in our sample

	No asthma n = 163	Asthma n = 38	t or χ^2	P value
Gender, M/F	126/37	29/9	0.02	.90
Age, yr (SD)	9.20 (1.9)	9.21 (1.9)	0.02	.98
Income group (<30,000$/ >30,000$)	32/130	11/27	1.54	.21
Ethnic origin (white/ non-white)	135/28	33/5	0.36	.55
Maternal smoking during pregnancy, no/yes	123/35	25/12	1.73	.19
Maternal alcohol consumption during pregnancy, no/yes	125/33	32/5	1.04	.31
Prematurity[a], no/yes	158/5	29/9	20.21	<.001
Obstetric complications[b], no/yes	35/121	4/33	2.51	.11
Stress during pregnancy, low/high	100/63	12/26	11.07	.001
Breastfeeding, no/yes	37/121	11/26	0.64	.42
Child's Behavior Checklist (CBCL) total *t*-score	67.81 (7.7)	66.61 (8.2)	0.85	.40
Conners' Parent *t*-score	70.76 (10.8)	70.41 (11.2)	0.17	.87

SD: standard deviation; M: male; F: female; yr: years of age

[a] Prematurity is defined as being born earlier than 37 weeks of gestation.

[b] Presence of obstetric complication defined as a rating of 4 or above on the McNeil-Sjöström scale, excluding prematurity and smoking during pregnancy.

logistic regression was restricted to complete case analysis (N=193). Analyses were performed using SPSS version 20.

Results

Chi-square analysis indicated a significantly higher presence of asthma in the present sample of children with ADHD compared to Quebec children, $\chi^2_{(1, N = 201)} = 15.37$, P<0.001. General characteristics of the sample are presented in Table 1. Chi-square analysis revealed that only the frequency of prematurity, obstetric complications and maternal stress during pregnancy were different between children with asthma compared to non-affected children (Table 1).

A logistic regression was conducted with asthma past or present as the dependent variable, and variables associated with asthma in the literature listed above as cofactors. Of those factors, only prematurity and stress during pregnancy significantly contributed to predict asthma ($\chi^2_{(8)}$=27.10, P<0.001). The odds ratio (OR) indicated that children who were born prematurely (before 37 weeks) were 10.58 times more likely to develop asthma (95% confidence interval (CI): 2.83-39.54) compared to children born full term (Table 2). In addition, children whose mothers experienced moderate or severe stress during pregnancy were 3.16 times more likely to develop asthma (95% CI: 1.36-7.33) compared to those exposed to milder stress. Overall prediction success was 83.9%. Of note is that there was no interaction between prematurity and stress during pregnancy in the development of asthma (p=0.12, OR:16.41, 95% CI:0.49-549.04).

Discussion

To our knowledge, this is the first study investigating the effects of factors including maternal stress during pregnancy on the risk of developing asthma specifically among children with ADHD. Our results suggest that children with ADHD born prematurely and/or whose mothers experienced moderate to extreme stress during pregnancy are at significantly higher risk of developing asthma than children born at term or those whose mothers were exposed to no or mild stress. Furthermore, we found that there is a significantly higher prevalence of asthma in our cohort of children with ADHD as compared to recent epidemiological data available for children in Quebec.

Given the numerous risk factors that have been associated with the onset of asthma in the general population, we examined possible variables that have been identified in the literature including: prematurity, maternal smoking during pregnancy, obstetrical complications, maternal stress during pregnancy, history of breastfeeding, family income, gender and age. Only prematurity and stress during pregnancy significantly predicted asthma. Parental history of asthma is considered as another risk factor for the development of asthma in children (Bjerg et al., 2007). However, this information is not available in our database. Contrary to other studies maternal smoking during pregnancy did not significantly predict asthma in our regression analysis possibly because our sample size was too small to separately examine heavy versus light smokers.

Similar to the present ADHD cohort study, several general population studies have identified prematurity as a risk

Table 2. Logistic regression of risk of developing asthma in children with ADHD

	p	Odds ratio	95% CI	
Age, yr (SD)	.91	0.99	0.80	1.22
Gender, M/F	.28	1.67	.66	4.20
Prematurity[a], no/yes	<.001	10.58	2.83	39.54
Stress during pregnancy, low/high	.01	3.16	1.36	7.33
Obstetric complications[b], no/yes	.53	1.47	0.44	4.90
Maternal smoking during pregnancy, no/yes	.87	1.09	0.41	2.89
Breastfeeding, no/yes	.71	0.82	0.30	2.27
Income group (<30,000$/ ≥30,000$)	.64	1.27	0.47	3.39

95% CI OR: 95% confidence interval of odds ratio; SD: standard deviation; M: male; F: female; yr: years of age

[a] Prematurity is defined as being born earlier than 37 weeks of gestation.

[b] Presence of obstetric complication defined as a rating of 4 or above on the McNeil-Sjöström scale, excluding prematurity and smoking during pregnancy.

factor for asthma. A retrospective Norwegian investigation of 7,925 children who sought care in a primary care setting suggested that late prematurity (34-36 weeks at birth) was associated with an increased severity of asthma. The authors also reported an increased risk of early childhood asthma in children with a low-normal gestational age (37-38 weeks) compared with gestational ages of more than 39 weeks (Goyal, Fiks, & Lorch, 2011). A systematic review and meta-analysis conducted by Jaakkola et al. (2006) found that children born prematurely (gestational age less than 37 weeks) have an approximately 7% higher risk of developing asthma compared with children born at term. Premature infants, especially if born at less than 35 weeks of pregnancy, often have breathing problems because their lungs are not fully developed. In order to reduce the risk of the baby developing lung problems such as neonatal respiratory distress syndrome, corticosteroids may be administered. However, Khalife et al. (2013) found an association between prenatal glucocorticoid exposure and ADHD-like behavioral scores at age eight. Furthermore, premature infants may require perinatal procedures. When activated by pain and stress, the hypothalamo-pituitary adrenal (HPA) axis induces an increase in cortisol secretion. Thus, infants who have undergone repeated painful procedures may develop an upregulated HPA axis with elevated cortisol levels after discharge from the hospital unit (Grunau et al. 2007).

In the expanding literature on the effects of maternal stress on fetal ontogeny and later risk of disease, our study adds novel findings that echo prior studies. DeMarco et al. (2012) conducted a retrospective analysis with a sample of 3854 children, investigating whether maternal 'stressful life event during pregnancy' (SLEP) influenced their children's risk of developing atopic diseases, including asthma. Following adjustment for potential confounders, children born to mothers who had experienced SLEP had a higher risk of asthma (OR: 1.71, 95% CI: 1.02–2.89) as well as other atopic diseases.

There exists a wide consensus regarding the numerous effects of environmental factors on fetal ontogeny. Stress experienced during early life may permanently alter the developing immune system, through a phenomenon known as perinatal programming. This concept refers to the organization (or imprinting) of physiological systems by nongenetic factors occurring early in life (Wright, 2008; Welberg & Seckl, 2001). The HPA axis and the autonomic nervous system (ANS) seem particularly susceptible to stress-induced programming. In this context, prenatal disruption of the maternal HPA axis has been linked to childhood asthma and allergy risk, although the mechanisms behind such associations remain uncertain (Wright, 2011). An increase in glucocorticoid production by the activation of the HPA axis is notably thought to modulate inflammatory gene expression (Martino & Prescott, 2011). Hormones triggered by maternal stress during pregnancy may also ultimately influence a predominance of T_H2 cells, associated with atopic asthma (Wright, 2008; von Hertzen, 2002). Finally, environmental exposures during critical periods of fetal development may induce epigenetic changes in gene expression, thereby modifying disease risk (Martino & Prescott, 2011). An extensive review on epigenetic dysregulations in the etiology of asthma is available elsewhere (De Planell-Saguer, Lovinsky-Desir, & Miller, 2014).

Strengths and Limitations

This study relies on a substantial sample size (n=201) of consecutively recruited children with ADHD. The wealth of clinical data available allowed us to control for numerous potential confounding factors. However, we could not include parental history of asthma in our analysis, since this information was not available in our database.

Another limitation of our study is related to its retrospective nature, which may predispose to recall bias. However, several strategies were implemented to address possible

drawbacks of retrospective design, including corroboration of the Kinney Medical and Gynecological Questionnaire results with medical and hospital obstetrical records. Also, in order to minimize the effects of subjectivity and recall bias, mothers were divided into two groups: those who had experienced no or mild stress during pregnancy versus moderate to severe stress. Stressors in the latter group were major life events that were easily placed in time and their stress effects were not in dispute, such as a divorce, death of a first-degree relative, incarceration of a spouse, or loss of a home due to fire. Of note is that there was a substantial prevalence of elevated maternal stress during pregnancy in our sample.

As for the history of asthma, the use of parental questionnaires may be perceived as a weakness in the design of our study. Nevertheless, a careful review of past medical history, including a specific question about asthma history, allergies, as well as current and past medications to treat the asthma was conducted through parental self-report questionnaires. A staff psychiatrist also assessed study participants in the setting of a clinical interview, including a thorough review of systems, and of medical history suggesting atopy. Furthermore, many epidemiological studies on children rely on parental-reported symptoms.

Conclusion

The results of this study suggest that children with ADHD have a higher prevalence of asthma than the general Quebec pediatric population. Our study shows that children with ADHD born prematurely and/or whose mothers experienced moderate to severe stress during pregnancy are at significantly higher risk to develop asthma, independently of other previously reported risk factors. These findings add to existing literature on the negative outcomes of maternal stress during pregnancy and prematurity, pointing to environmental remediation as an important preventative measure.

More research is needed in order to elucidate the pathophysiological impact of prematurity and/or maternal stress during pregnancy and later development of atopic diseases like asthma and behavioral disorders such as ADHD.

Acknowledgements/Conflicts of Interest

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