Archival Report

Biological Psychiatry

Attention-Deficit/Hyperactivity Disorder in Offspring of Mothers With Inflammatory and Immune System Diseases

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ABSTRACT

BACKGROUND: Prenatal inflammatory mechanisms may play a role in the pathogenesis of psychiatric disorders and could be relevant for attention-deficit/hyperactivity disorder (ADHD). We investigated maternal chronic somatic diseases with immune components as possible risk factors for ADHD in offspring.

METHODS: We performed a population-based nested case-control study by linking data from longitudinal Norwegian registers. We included all individuals born during the period 1967–2008 and alive at record linkage (2012). Individuals receiving ADHD medication during the years 2004–2012 were defined as patients with ADHD (N = 47,944), and all remaining individuals (N = 2,274,713) were defined as control subjects. The associations between maternal diseases and ADHD in offspring were analyzed using logistic regression models.

RESULTS: The following chronic diseases with immune components were related to ADHD in offspring: multiple sclerosis (adjusted odds ratio [OR] = 1.8; 95% confidence interval [CI] = 1.2–2.5), rheumatoid arthritis (adjusted OR = 1.7; 95% CI = 1.5–1.9), type 1 diabetes (adjusted OR = 1.6; 95% CI = 1.3–2.0), asthma (adjusted OR = 1.5; 95% CI = 1.4–1.6), and hypothyroidism (adjusted OR = 1.2; 95% CI = 1.1–1.4). In contrast, chronic hypertension and type 2 diabetes showed no significant associations. Estimates were almost unchanged with additional adjustment for parental ADHD, infant birth weight, and gestational age. Although point estimates for male and female offspring were different for some diseases (e.g., maternal asthma [adjusted OR = 1.7; 95% CI = 1.5–1.8 for female offspring and adjusted OR = 1.5; 95% CI = 1.4–1.6 for male offspring]), none of the associations differed significantly by offspring sex.

CONCLUSIONS: Several maternal somatic diseases with immune components were found to increase the risk of ADHD in offspring. The associations could involve several causal pathways, including common genetic predisposition and environmental factors, and increased insight into the mechanisms behind these relationships could enhance our understanding of the etiology of ADHD.

Keywords: ADHD, Attention-deficit/hyperactivity disorder, Immune disease, Inflammatory disease, Maternal effects, Risk factors

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects children and adults worldwide, with prevalence estimates ~5% in children (1) and 3% in adults (2). The prevalence varies among studies; in a Norwegian study of children 8–10 years old, it was estimated to be 1.7% (3). The disorder is two to three times more frequent in boys than girls (4), although the sex distribution becomes more equal with age (5). The etiology of ADHD is complex, involving interactions between genetic and environmental factors, and many risk pathways may lead to its clinical features (6).

Previous studies described several prenatal and perinatal risk factors for ADHD. Low birth weight (7–12), preterm birth (8,9,13–16), and small size for gestational age (8,16) have consistently been related to an increased risk of ADHD or ADHD symptoms. Exposure to maternal smoking (17) and other substances in utero (6) also have been reported to be associated with increased risk of ADHD. Furthermore, associations with ADHD in offspring have been found for some maternal medical conditions, including obesity (18) and epilepsy (8). It has been hypothesized that ADHD may be caused by an exaggerated central nervous system inflammatory response in the fetus caused by maternal inflammation, such as in allergy or autoimmune disease (19). It is difficult to draw conclusions about causal pathways, as associations between maternal diseases and ADHD in offspring can involve several different, partly overlapping, causal pathways. Common genetic predisposition, environmental factors such as maternal medication exposures, and fetal inflammatory response are examples of such causes. Because few studies have

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evaluated maternal immune system diseases, we investigated whether such diseases were associated with ADHD in offspring using data from nationwide registers in Norway. Additionally, we assessed whether these risk factors differed by patient's sex.

METHODS AND MATERIALS

This study was approved by the Norwegian Data Protection Authority, the Norwegian Directorate of Health, and the Regional Committee for Medical and Health Research Ethics (2011/2272). The data were treated anonymously, and so no further consent was required.

We performed a population-based nested case-control study by linking information from the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Database (NorPD), and the National Educational Database. In a sensitivity analysis, we also included data from the Norwegian Patient Registry.

The nationwide MBRN was established in 1967 and contains information on nearly 2.6 million births up to 2012. The registration is based on compulsory notification and includes information on all live births and fetal losses/stillbirths from 16 weeks of gestation. A standardized form is used to document information on maternal health before and during pregnancy, complications during pregnancy and delivery, and birth outcomes. For the years 1967–1998, information was mainly documented as free text specifications to items such as "Maternal health before pregnancy," "Maternal health during pregnancy," "Complications in relation to birth," and "Infant outcomes." A more detailed documentation form, introduced in 1999, included information on maternal smoking habits and check boxes for specific conditions in addition to free text (20). The NorPD covers all prescribed drugs dispensed to individuals in Norway since 2004. From 2008, NorPD includes diagnostic codes (ICD-10/International Classification of Primary Care, Second edition) for reimbursed drugs (21). The level of education of all Norwegian inhabitants from 16 years of age is registered annually in the National Education Database. The Norwegian Patient Registry provides information on diagnoses of all patients having contact with specialist health services from 2008.

Study Population and Variable Information

Record linkage was established by using the personal identity number unique to every Norwegian resident. This study included all individuals born from 22 weeks of gestation or with birth weight at least 500 g in Norway during the period 1967–2008 who were still alive at record linkage in 2012 (N = 2,322,657).

Cases in this study consisted of all registered individuals in MBRN born during the period 1967–2008 who had been prescribed and dispensed ADHD medications during the years 2004–2012 and were >3 years old at last prescription.

The dispensed and reimbursed ADHD medications methylphenidate (Anatomical Therapeutic Chemical Classification System [ATC] code N06BA04), atomoxetine (ATC code N06BA09), and racemic amphetamine (ATC code N06BA01) were extracted from the NorPD. The use of ADHD medication is restricted in Norway; medical treatment of ADHD is initiated only after thorough assessment of the patient by a specialist in psychiatry or child psychiatry. Dexamphetamine (ATC code N06BA02) was off label in Norway during the study period and is not used as a first-option treatment and therefore was not included in our case definition. Drugs used to treat ADHD may also be used for narcolepsy. Using the reimbursement codes from 2008, we found that 117 individuals (1.4%) were dispensed stimulant medication with the indication narcolepsy, and these were excluded from the case group. Thus, for patients who were dispensed medicine in the period 2004–2008 only, there may be a small number of individuals with narcolepsy left in the case group.

The control group included all registered individuals in MBRN born during the period 1967–2008 and alive at record linkage who had not been dispensed ADHD medication during the period 2004–2012. The 117 individuals who were dispensed stimulant drugs for narcolepsy in the period 2008–2012 were included in the control population (N = 2,274,713). Thus, by design, the control group included people with a diagnosis of ADHD who did not receive ADHD medication or who had used (and stopped using) ADHD medication before 2004 when the NorPD was established.

Maternal educational level was used as a measure for socioeconomic level and grouped in three categories: low (<10 years), medium (10–12 years), and high (>12 years).

Description of Variables

As potential prenatal risk factors for ADHD, we studied the following maternal chronic somatic diseases, all with inflammatory or immune components of pathologic relevance: multiple sclerosis, asthma, rheumatoid arthritis, hypothyroidism, hyperthyroidism, and pregestational type 1 diabetes. Pregestational type 2 diabetes and chronic hypertension were also included. Because we assumed that immunologic/inflammatory mechanisms are less strongly involved in these conditions, they were included to serve as contrasting chronic diseases in the analyses. We chose the diseases included in the analyses using several criteria. Our focus was immune system diseases, and we selected diseases for which the MBRN registration was previously validated (pregestational type 1 and 2 diabetes, rheumatic arthritis, asthma) (20,22), diseases that were previously described in the literature with data from MBRN (multiple sclerosis) (23–25), diseases for which the MBRN notification form from 1999 had specific check boxes (asthma, diabetes type 1 and 2, rheumatic arthritis and chronic hypertension), and diseases for which the MBRN reported significantly increasing time trends in prevalence and for which associations with ADHD in offspring was previously discussed (thyroid disorders) (26–29). The maternal diseases were diagnosed before or during pregnancy for the target individual. Pregestational diabetes, without subtyping, has been registered in the MBRN from 1967 and specified as type 1 and type 2 since 1988 (n = 32,984 cases, n = 1,113,011 controls).

Statistical Analyses

Analyses were performed with PASW Statistics 18 (SPSS Hong Kong, Quarry Bay, Hong Kong) and Stata version 13