Brain, Behavior, and Immunity 44 (2015) 100–105

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Maternal hospitalization with infection during pregnancy and risk of autism spectrum disorders

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ARTICLE INFO

Article history:
Received 8 July 2014
Received in revised form 15 August 2014
Accepted 2 September 2014
Available online 16 September 2014

Keywords:
Autism
Infection
Cytokines
Epidemiology

ABSTRACT

Animal models indicate that maternal infection during pregnancy can result in behavioral abnormalities and neuropathologies in offspring. We examined the association between maternal inpatient diagnosis with infection during pregnancy and risk of ASD in a Swedish nationwide register-based birth cohort born 1984–2007 with follow-up through 2011. In total, the sample consisted of 2,371,403 persons with 24,414 ASD cases. Infection during pregnancy was defined from ICD codes. In the sample, 903 mothers of ASD cases (3.7%) had an inpatient diagnosis of infection during pregnancy. Logistic regression models adjusted for a number of covariates yielded odds ratios indicating approximately a 30% increase in ASD risk associated with any inpatient diagnosis of infection. Timing of infection did not appear to influence risk in the total Swedish population, since elevated risk of ASD was associated with infection in all trimesters. In a subsample analysis, infections were associated with greater risk of ASD with intellectual disability than for ASD without intellectual disability. The present study adds to the growing body of evidence, encompassing both animal and human studies, that supports possible immune-mediated mechanisms underlying the etiology of ASD.

1. Introduction

Little is known about the etiology of autism spectrum disorders (ASD), but there is suggestive evidence for the role of environmental exposures during critical periods of early neurodevelopment (Newschaffer et al., 2007). Prenatal infection is a plausible risk factor for ASD, given that the teratogenic effect of prenatal infections such as rubella, cytomegalovirus or *Toxoplasma gondii* on the central nervous system is well established (Johnson, 1994). Numerous animal studies demonstrate that prenatal or early postnatal infections can result in both acute and persistent neurological and behavioral abnormalities in offspring resembling autistic traits or schizophrenia (Asp et al., 2009; Meyer et al., 2007; Patterson, 2011). However, the validity of such animal models for human ASD is uncertain.

The first studies suggesting an association of prenatal infection with ASD focused on viruses with affinity to the CNS based on the hypothesis of a direct neurotoxic effect. Epidemiological studies of small samples suggested that rubella (Chess et al., 1978; Deykin and MacMahon, 1979), measles, mumps, and influenza (Deykin and MacMahon, 1979) were associated with ASD. More recently, epidemiological studies have expanded infectious exposures to a wide range of viruses and also other pathogens including bacteria. The largest study of over 10,000 ASD cases drawn from Danish electronic health registers reported that maternal hospitalization for viral infection in the first trimester and any infection or bacterial infection in the second trimester were associated with increased ASD risk (Atladottir et al., 2010). However, epidemiological findings have not consistently found evidence of increased ASD risk with infection. For example, a California study of 407 ASD cases reported that hospitalization with infection was associated with increased risk (Zerbo et al., 2013), while a Swedish study of 1216 ASD cases found no such evidence (Buchmayer et al., 2009),

In order to build the evidence base concerning prenatal infection and ASD risk, additional epidemiological studies are necessary.

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http://dx.doi.org/10.1016/j.bbi.2014.09.001
0889-1591/

Moreover, as different subtypes of ASD may have different environmental components (Frazier et al., 2014), it is important to examine whether prenatal infection differentially influences ASD subtype risk (with or without intellectual disability). Here, we examined whether maternal hospitalization with infection during pregnancy, type of infection, and timing of infection influences risk of ASD in the largest study to-date. In a subsample of the Swedish population with information on ASD co-morbid with or without intellectual disability, we further examined the associations of prenatal infection with these different subtypes of ASD (Szatmari et al., 2007).

2. Methods

2.1. Overview

The Swedish population register system retains routinely collected health and sociodemographic data on the entire population of Sweden. The registers are cross-linked via each person's unique national registration number assigned to all Swedish residents at birth or upon migration to Sweden (Ludvigsson et al., 2009). The ascertainment of ASD in the total Swedish population is based on data from national registers primarily covering inpatient admissions. In the subsample study of ASD with or without co-morbid intellectual disability, we studied a subsample of the total Swedish population, the Stockholm Youth Cohort (SYC), for which ascertainment of ASD is based on national register data in addition to regional register data from outpatient, specialist, and treatment centers in Stockholm County. Consequently, while the total Swedish population sample is substantially larger, the SYC subsample has better ASD ascertainment and subtype information regarding comorbid intellectual disability.

2.2. Study sample and ASD case ascertainment

The sample in this study consisted of all individuals born in Sweden 1984–2007 and followed until December 31, 2011. All data are derived from linkages to national registers held by Statistics Sweden and the National Board of Health and Welfare. The National Patient Register contains data on all inpatient care in Sweden since 1973 and includes outpatient specialist care since 2001. ASD case status as of December 31, 2011, was defined as a recorded diagnosis of ICD-9 (299) or ICD-10 (F84) in the National Patient Register. A recent medical record review of autism in the National Patient Register following a CDC validation protocol confirmed the presence of DSM-IV autism in 83 of 88 persons (94.3%) (Ludvigsson et al., 2013). In total, 2,385,678 persons were in the 1984–2007 birth cohorts. After exclusion of observations with missing covariate data, the final sample consisted of 2,371,403 persons, with 24,414 identified ASD cases.

The Stockholm Youth Cohort is a register-based study with continuous enrollment comprising all individuals who were ever resident in Stockholm County as children (Idring et al., 2012; Magnusson et al., 2012). All data are derived from linkages to national registers held by Statistics Sweden and the National Board of Health and Welfare, as well as regional registers held by the Stockholm County Council. In total, 501,271 persons were in the 1984–2007 birth cohorts and resident in Stockholm County for $\geqslant$4 years. ASD case status as of December 31, 2011 was ascertained according to a validated case-finding approach covering all pathways to ASD diagnosis and care in Stockholm County, described in detail elsewhere (Idring et al., 2012). In brief, ASD case status was described following ICD-9 (299), ICD-10 (F84), and DSM-IV (299) classifications using (1) the National Patient Register; and regional registers including (2) the Habilitation Register; (3) the Clinical Database for Child and Adolescent Psychiatry; (4) the VAL database recording all inpatient and outpatient health services usage in Stockholm County since 1997. Determination of intellectual disability was based on ICD-9 (317–319), ICD-10 (F70–F79), and DSM-IV (317–319) classifications and supplemented with the Habilitation Register, which categorizes service recipients as having autism with or without intellectual disability. Expert review of medical records for 177 ASD cases indicated that 96% were consistent with a diagnosis of ASD (Idring et al., 2012). After exclusion of observations with missing covariate data, the final sample consisted of 496,993 persons, with 9585 identified ASD cases.

2.3. Maternal hospitalization with infection during pregnancy

Information on maternal hospital admissions with diagnoses of infection during the pregnancy period was obtained from ICD-8, -9, and -10 codes in the National Patient Register. The pregnancy period was calculated using the gestational age based on early second trimester ultrasound for 95% of women (Hogberg and Larsson, 1997) or first day of the last menstrual period for the remainder. Hospital admission records in the National Patient Register list one primary diagnosis and up to seven secondary diagnosis codes.

We considered a prenatal infection to have occurred if an ICD code for infection was found in the primary or secondary codes. The rationale for this was based on the consideration that regardless of whether a pregnant woman has a primary or secondary diagnosis of an infection, the fetus is still exposed to the infection. In addition, primary inpatient diagnoses for infection potentially reflect more severe infections and may not well-represent cases that resolve without treatment. By examining all recorded infections regardless of primary or secondary diagnosis, we were able to include some infections that would be more likely to not require hospitalization, potentially increasing the generalizability of results. This infectious exposure definition was used by Zerbo et al., although Atladottir et al. considered only primary diagnoses of infection. One potential concern with including both primary and secondary diagnoses of infection is that the primary diagnosis, whatever it may be, may confound an association observed between infection and ASD. Therefore, we adjusted for hospitalizations during pregnancy and performed two sensitivity analyses described below, examining robustness to confounding, as well as repeating analyses considering only primary inpatient diagnoses of infection during pregnancy.

ICD codes for infection are listed in Supplementary Table 1. We categorized infections according to type, timing, and site. Types of infection were: (1) *Any infection* – bacterial, viral, other and unknown regardless of site of infections (2) *Bacterial infection*; (3) *Viral infection*; and (4) *Other infection* (infection from primarily unknown agents as well as protozoa, helminth, or fungi). Timings of infection were assessed according to first, second, or third trimester of pregnancy. To be able to compare with previous work, sites of infection were categorized following (Atladottir et al., 2010; Zerbo et al., 2013), and included: CNS, gastrointestinal, genitourinary, respiratory, and skin infections.

2.4. Covariates

Covariates considered in analyses were identified *a priori* from the literature or prior work as being risk factors for ASD. Biological parents and dates of birth were identified from the Multigeneration Register. Following our previous work (Idring et al., 2014), maternal age and birth year were centered and entered into models as quadratic terms, and paternal age was entered as a continuous term. The Integrated Database for Labor Market Research provided information on individual-level disposable family income at time of birth, calculated after deductions of taxes and adjusted