Schizophrenia Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Maternal exposure to sexually transmitted infections and schizophrenia among offspring

Keely Cheslack-Postava [a], Alan S. Brown [a,b,*], Roshan Chudal [c], Auli Suominen [c], Jukka Huttunen [c], Helja-Marja Surcel [d], Andre Sourander [a,c,e]

[a] Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, United States
[b] Department of Epidemiology, Columbia University Mailman School of Public Health, 722 West 168th Street, New York, NY 10032, United States
[c] Department of Child Psychiatry, Faculty of Medicine, University of Turku, Turku, Finland
[d] National Institute for Health and Welfare, Oulu, Finland
[e] Department of Child Psychiatry, Turku University Hospital, Turku, Finland

ARTICLE INFO

Article history:
Received 5 January 2015
Received in revised form 1 May 2015
Accepted 4 May 2015
Available online xxxx

Keywords:
Schizophrenia
HSV-2
Chlamydia
Prenatal infection
Epidemiology

ABSTRACT

Animal models and epidemiologic studies suggest that prenatal maternal infection, and sexually transmitted infection (STI) in particular, is associated with an increased risk of schizophrenia in the offspring. However, findings from prior research studies on common infections, including herpes simplex virus type 2 (HSV-2) and *Chlamydia trachomatis* (*C. trachomatis*) have been inconsistent. To investigate these associations, we conducted a case–control study nested in the population-based Finnish Prenatal Study of Schizophrenia. Using linked national registries, 963 cases with schizophrenia (ICD-10 F20) or schizoaffective disorder (ICD-10 F25), and 963 matched controls were identified from among all persons born between 1983 and 1998 in Finland. HSV-2 IgG antibody levels were quantified in archived maternal serum samples drawn during pregnancy. Mothers of 16.4% of cases versus 12.6% of controls were HSV-2 seropositive. Mean levels of maternal HSV-2 IgG were marginally higher among cases than controls (index values of 0.98 versus 0.86; $p = 0.06$). The unadjusted odds ratio (OR) of maternal HSV-2 IgG seropositivity was 1.33 (95% confidence interval (CI) = 1.03–1.72, $p = 0.03$). Following adjustment for covariates, the relationship was attenuated (OR = 1.22, CI = 0.93–1.60; $p = 0.14$). In an exploratory analysis of another STI, *C. trachomatis* antibodies were measured in a subsample of 207 case–control pairs drawn from the cohort. The proportions of subjects that were seropositive and the mean levels of *C. trachomatis* antibodies were similar for cases and controls. This study does not support a strong association of HSV-2 or *C. trachomatis* IgG antibodies in maternal serum during early to mid-gestation with the development of schizophrenia in the offspring.

1. Introduction

Epidemiologic studies and animal models of maternal immune activation provide evidence that prenatal maternal infection is a risk factor for the development of schizophrenia in the offspring (Brown and Patterson, 2011). Specific infectious agents including rubella (Brown et al., 2001), influenza (Brown et al., 2004), and *Toxoplasma gondii* (Brown et al., 2005; Mortensen et al., 2007) have been linked to schizophrenia. Maternal diagnosis with genital and reproductive infections during the periconceptional period, as reported in obstetric records, was associated with a fivefold increased risk of schizophrenia among members of a cohort born between 1959 and 1966 in California (Babulas et al., 2006). The infections included endometritis, cervicitis, pelvic inflammatory disease, vaginitis, syphilis, condylomata, "venereal disease," and gonorrhea, but whether the association was attributable to particular pathogens was not determined. Therefore, investigating maternal exposure to specific common genital and reproductive infections, such as those that are sexually transmitted, may yield additional risk factors for schizophrenia. Two of the most common sexually transmitted infections (STIs) are herpes simplex virus type 2 (HSV-2) and *Chlamydia trachomatis* (*C. trachomatis*).

HSV-2 infection during pregnancy has known teratogenic effects, including on cognitive development (Adams Waldorf and McAdams, 2013), and has been investigated with respect to risk for schizophrenia. However, results of these studies have been inconsistent, with some (Buka et al., 2001, 2008; Mortensen et al., 2010) reporting positive associations, and others (Brown et al., 2006; Mortensen et al., 2007; Blomstrom et al., 2012) finding no relationship. This may be due in part to low participation rates (Blomstrom et al., 2012); the use of neonatal biosamples in some studies (Mortensen et al., 2007, 2010; Blomstrom et al., 2012) versus maternal biosamples in others (Buka

* Corresponding author at: New York State Psychiatric Institute, 1051 Riverside Drive Unit 23 (U.S. Postal/regular mail), Kolb Annex Room 125(FedEx/other courier service), New York, NY 10032, United States. Tel.: +1 646 774 6417; fax: +1 646 774 6408.
E-mail address: asb11@columbia.edu (A.S. Brown).

http://dx.doi.org/10.1016/j.schres.2015.05.012
0920-9964/

et al., 2001, 2008; Brown et al., 2006); and limited numbers of cases (Buka et al., 2001; Brown et al., 2006; Blomstrom et al., 2012). The only prior studies that examined prenatal maternal serum samples (Buka et al., 2001, 2008; Brown et al., 2006) used specimens collected late in pregnancy and had modest sample sizes.

C. trachomatis is the most common bacterial STI in the U.S. (Darville, 2006) and has been associated with adverse pregnancy outcomes including spontaneous abortion, stillbirth and preterm birth, in addition to conjunctivitis and respiratory infection in the neonate (Mardh, 2002). To our knowledge, only one small study has previously examined whether the presence of *C. trachomatis* antibodies in maternal prenatal serum is related to offspring schizophrenia diagnosis, finding no significant difference between cases and controls (Buka et al., 2001).

In order to overcome the limitations of the previous studies of HSV-2 and schizophrenia to date, we used archived maternal serum samples drawn during early to mid-gestation from the population-based Finnish Prenatal Study of Schizophrenia (FIPS-S), a large, national birth cohort study. For this purpose, we measured IgG antibody specific to HSV-2 in maternal serum specimens drawn during pregnancy for 963 case–control pairs. Measures for maternal *C. trachomatis* IgG were also obtained, though in a limited subsample of 207 case–control pairs, due to funding constraints. Nonetheless, this was a potentially important exploratory analysis, given that this common STI has been investigated in only a limited way in relation to schizophrenia.

2. Methods

2.1. Study description

Study subjects were identified through the Finnish Prenatal Study of Schizophrenia (FIPS-S), a nested case–control study based on a national cohort of all births in Finland from 1983 to 1998, and followed up until 2009. The data used in this study were derived from national registries, the Finnish Hospital Discharge Register (FHDR), the Finnish Medical Birth Register (FMBR), and the Finnish Central Population Register (CPR), and Statistics Finland (described below), which were linked using the unique personal identity codes given to every Finnish resident.

The FHDR is maintained by the National Institute of Health and Welfare, and includes all public and private inpatient diagnoses since January 1, 1967, and outpatient diagnoses since January 1, 1998. Diagnoses in the FHDR are based on the International Classification of Diseases and Related Health Problems (ICD). Previous validation studies have reported that 87% (Arajarvi et al., 2005) and 93% (Makikyro et al., 1998) of patients with register-based schizophrenia spectrum diagnoses also met criteria for schizophrenia spectrum disorders following research reviews of medical records.

The FMBR is also maintained by the National Institute of Health and Welfare, and includes comprehensive data on the pre-, peri-, and neonatal periods up to seven days following delivery for all births in Finland. It was established in 1987. The FCPR contains basic information about Finnish citizens and foreign citizens residing permanently in Finland, including name, personal identity code, address, municipality of residence, country and date of immigration/emigration, mother language, family relations and date of birth and death. A fourth registry, Statistics Finland, was used to identify the level of urbanicity of birth locations.

Serum samples were drawn for the purpose of prenatal screening from over 98% of the mothers of cohort members during early to mid-pregnancy, and subsequently archived at −25 °C in a single, centralized repository. These samples were linked to the other registries using the personal identity codes.

2.2. Identification of subjects

A total of 1514 cases with a diagnosis of schizophrenia (ICD-10 F20) or schizoaffective disorder (ICD-10 F25) (henceforth referred to collectively as "schizophrenia") occurring through 2009 were identified. For each case, one control was randomly selected from the cohort, and matched on date of birth (+/− one month), sex, and having been alive and residing in Finland at the time of the case diagnosis. Control subjects were required to be without diagnoses of schizophrenia, other non-affective psychotic disorders, or bipolar disorder at the time of case diagnosis. For HSV-2, all case–control pairs with adequate quantities of sera for analysis were assayed. Because the *C. trachomatis* analysis was exploratory, a limited sample of case–control pairs was selected at random from those with sera available.

2.3. Laboratory analyses

IgG class antibodies to HSV-2 in sera were measured by HerpeSelect® 2 ELISA (Focus Diagnostics, Cypress, California, USA). The sensitivity and specificity of the assay are 96.1% and 97.0%, respectively. The results are expressed as index values relative to the cut-off calibrator, calculated by dividing the specimen optical density (OD) values by the mean of the cut-off calibrator absorbance values. The index values are interpreted as follows: >1.10, positive; ≥0.90 and ≤1.10, equivocal; and <0.90, negative. *C. trachomatis* specific IgG antibodies were analyzed using ELISA kits (AniLabsystems Ltd, Vantaa, Finland). A peptide-based EIA test is considered species-specific with minimal cross-reactivity with other *Chlamydia* species. The reproducibility of the test is high (SD 0.061, coefficient of variation 4.9%). Results are expressed as absorbance of the sample, with absorbance values interpreted as follows: >1.0, positive; >0.6 and <1.0, equivocal; and <0.6, negative.

2.4. Covariates

Covariates were selected for inclusion based on potential associations with schizophrenia and with maternal prenatal IgG seropositivity to HSV-2 and *C. trachomatis*. These variables included maternal age, paternal age, maternal parity, maternal education, paternal education, maternal or parental history of psychiatric disorders (schizophrenia, non-affective psychosis, affective disorders, any psychiatric disorder), gestational age, gestational week of blood draw, multiple versus singleton birth, municipality of birth, province of birth, and maternal immigration status. Covariates were categorized as shown in Table 1.

2.5. Statistical analysis

Bivariate associations of the covariates with: a) schizophrenia, and with b) HSV-2 and *C. trachomatis* positivity among the controls were examined using χ^2 or t-tests. First, preliminary analyses examining the association between antigen-specific IgG and schizophrenia diagnosis were conducted using all observations. Mean levels of HSV-2 and *C. trachomatis* IgG were compared between cases and controls using paired t-tests, and the unadjusted distributions of seropositivity status (positive, equivocal, negative) were compared between cases and controls using conditional logistic regression for matched pairs.

The main analyses focused on the 98.1% of observations that were unambiguously seropositive or negative for maternal HSV-2 IgG. The rationale for excluding observations with equivocal seropositivity from these analyses was to reduce potential bias due to misclassification of the exposure. HSV-2 IgG was considered as a dichotomous variable (positive versus negative) and as a continuous variable (log-transformed due to the skewed distribution). For the analysis of HSV-2 IgG as a continuous variable, seronegative observations were set to a value of 0 because the ELISA measures are not interpretable for seronegative samples. Conditional logistic regression models were fit both without, and following adjustment for potential confounders. Covariates were considered potential confounders if they were associated with both schizophrenia and HSV-2 seropositivity, and were not in a potential causal pathway between the two (Greenland and Rothman, 2008).

Please cite this article as: Cheslack-Postava, K., et al., Maternal exposure to sexually transmitted infections and schizophrenia among offspring, Schizophr. Res. (2015), http://dx.doi.org/10.1016/j.schres.2015.05.012