



Association of maternal genital and reproductive infections with verbal memory and motor deficits in adult schizophrenia [☆]

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ABSTRACT

Maternal exposure to genital and reproductive infections has been associated with schizophrenia in previous studies. Impairments in several neuropsychological functions, including verbal memory, working memory, executive function, and fine-motor coordination occur prominently in patients with schizophrenia. The etiologies of these deficits, however, remain largely unknown. We aimed to assess whether prospectively documented maternal exposure to genital/reproductive (G/R) infections was related to these neuropsychological deficits in offspring with schizophrenia and other schizophrenia spectrum disorders. The cases were derived from a population-based birth cohort; all cohort members belonged to a prepaid health plan. Cases were assessed for verbal memory, working memory, executive function, and fine-motor coordination. Compared to unexposed cases, patients exposed to maternal genital/reproductive infection performed more poorly on verbal memory, fine-motor coordination, and working memory. Stratification by race revealed associations between maternal G/R infection and verbal memory and fine-motor coordination for case offspring of African-American mothers, but not for case offspring of White mothers. Significant infection-by-race interactions were also observed. Although independent replications are warranted, maternal G/R infections were associated with verbal memory and motor function deficits in African-American patients with schizophrenia.

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1. Introduction

Maternal exposure to genital/reproductive (G/R) infection is a known risk factor for congenital central nervous system anomalies (Kropp et al., 2006; Remington et al., 2006; Engman et al., 2008), and has been associated with schizophrenia in previous studies. In a follow-up of the Child Health and Development Study (CHDS) birth cohort, periconceptional exposure to maternal G/R infections was related to a significantly increased risk of schizophrenia and other schizophrenia spectrum disorders (SSD) among offspring (Babulas et al., 2006). Among G/R infections, herpes simplex virus type 2 (HSV-2), which is shed at genital sites, is one of the most common sexually transmitted diseases.

Previous studies have examined the relationship between maternal exposure to HSV-2 and risk of psychosis and schizophrenia in adult offspring. In the first two, based on the National Collaborative Perinatal Project (NCPP) birth cohort, elevated maternal IgG antibody levels to HSV-2, and seropositivity to this infection were related to a significantly increased risk of psychosis in adult offspring (Buka et al., 2001, 2008). In a third study, from the CHDS cohort, however, no relationships were observed between HSV-2 IgG antibody levels or seropositivity to this virus and risk of SSD (Brown et al., 2006). In particular, the NCPP birth cohorts in the latter study from this sample included a greater number of African-Americans than the CHDS cohort, and African-Americans have a considerably higher prevalence of HSV-2 infection, which in that study was over four times higher than in Caucasians (Buka et al., 2008). Other explanations for the differences in findings between the two birth cohorts are discussed in detail in Brown and Derkits (2010).

Perinatal exposure to HSV-2 is associated with adverse neuropsychiatric outcomes during childhood, including mental retardation, impaired attention, communication and language deficits, and gross and fine motor disability (Kropp et al., 2006; Engman et al., 2008). Other

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maternal G/R infections, including syphilis (Ingall and Sanchez, 2001) have also been associated with impaired neurocognitive outcomes among offspring. Impairment in neuropsychological functions is one of the hallmark features of schizophrenia and plays a considerable role in social and occupational impairment in this disorder (Goldberg et al., 2003; Kraus and Keefe, 2007). Hence, G/R infections during pregnancy may play a role not only in risk of schizophrenia but also in neurocognitive deficits in this disorder. Hence, in the present study, we investigated the relationship between maternal seropositivity to HSV-2 and other maternal G/R infections and neurocognitive outcomes in offspring with SSD from a population-based birth cohort. The sample comprised schizophrenia cases from the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study, who were administered a comprehensive neuropsychological test battery. All cases were clinically stable adult schizophrenia outpatients who had been followed up for this disorder in an earlier study in a large birth cohort (Susser et al., 2000). Subjects who participated in the DIBS study represented a subsample of subjects who were followed up in the earlier study. The study featured prospectively collected data on GR infection that was acquired from testing of maternal sera for HSV-2 antibody and maternal obstetric records by physicians.

Based upon previous studies of neurocognition and neuromotor impairment in schizophrenia and in follow-up studies of maternal G/R infections, our evaluation focused on the relationship between this exposure and performance in 4 domains of functioning: verbal memory, working memory, executive function, and fine-motor coordination. Given the small number of controls with serologic data, the analysis was restricted to the SSD cases.

2. Methods

The methods of the DIBS study have been extensively described in a previous publication (Brown et al., 2009), which includes a flow diagram of the recruitment and selection of subjects for the DIBS study. Hence, these methods will be only summarized here.

Subjects were derived from a follow-up study of schizophrenia among offspring of mothers who were enrolled in the Child Health and Development Study (CHDS), a large birth cohort, from 1959 to 1966 (van de Berg, 1984). Nearly every pregnant woman received obstetric care from the Kaiser Permanente Medical Care Plan (KPMCP) in Alameda County, California. There were 12,094 live births in 1981, the beginning of case ascertainment from the KPMCP databases. Maternal sera were collected during pregnancy from virtually all mothers who participated in the CHDS.

2.1. Ascertainment and diagnosis

These methods are elaborated in detail in previous publications (Susser et al., 2000; Brown et al., 2004), and are summarized here. The main outcome was schizophrenia and other schizophrenia spectrum disorders (SSD), which was defined as: schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder not otherwise specified, and schizotypal personality disorder, in accord with previous studies (Kendler et al., 1995). Case ascertainment was based on computerized record linkage between the CHDS and KPMCP identifiers from inpatient and outpatient databases. Patients with ICD-9 diagnoses of 295–299 and/or patients treated with antipsychotics were administered the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) by clinicians with a minimum of a master's degree in a mental health field trained to reliability. Psychiatric diagnoses were made by DSM-IV criteria following consensus of three experienced research psychiatrists. Diagnostic chart reviews were conducted for potential cases who were not interviewed. These procedures resulted in 71 total SSD cases. There were 38 cases with schizophrenia, 15 with schizoaffective disorder, and 11 with other schizophrenia spectrum disorders. Therefore, the vast majority of cases had either schizophrenia or schizoaffective disorder.

2.2. Assessment of exposure to maternal genital/reproductive infections

We utilized two previously established sources of data on maternal G/R infection in the CHDS cohort. The first was based on seropositivity to IgG antibody for HSV-2. As in our previous study in this cohort (Brown et al., 2006), HSV-2 was quantified using the HerpesSelect ELISA assay (Focus Technologies, Cypress, CA). The second was systematically generated from CHDS records from physician diagnoses made during obstetric and medical visits to KPMCP, which provided treatment to all gravidas in the CHDS. All maternal G/R infections present in the database, and documented after 6 months prior to conception throughout pregnancy were included; these consisted of endometritis, cervicitis, pelvic inflammatory disease, vaginitis, syphilis, condylomata, "venereal disease," and gonorrhea (Babulas et al., 2006). We included G/R infections occurring at any time

during pregnancy, rather than only during the gestational period associated with schizophrenia in our previous study (Babulas et al., 2006) since we aimed to examine whether G/R infection both during and outside of that gestational period would be associated with impaired neurocognitive function. Subjects were considered to have been exposed to maternal G/R infection based on seropositivity to HSV-2 or diagnosis with any of the documented G/R infections. The rationale for combining these two definitions of exposure was threefold: first, HSV-2 is nearly always a G/R infection; second, all of these infections are localized to the maternal reproductive organs, with proximity to the fetal compartment, suggesting that they operate by common mechanisms to alter fetal brain development; third, combining these categories of infection improved statistical power. The prevalence of HSV-2 seropositivity was 25% and of database derived maternal G/R infection was 13% in the cases of the present study, excluding cases classified with both infections (12%) (see Section 2.3 for description of cases).

2.3. Ascertainment of the DIBS study sample

The DIBS study is a nested case-control study based on the larger schizophrenia follow-up of the CHDS cohort described above. All subjects who met eligibility criteria were targeted for neuropsychological assessments. Subjects with major medical illnesses including neurologic disorders were excluded; see (Brown et al., 2009) for more details. Hospitalized cases or those deemed to be too severely psychotic for neurocognitive testing were also excluded. Selection of subjects was not determined by maternal antibody titers or maternal medical conditions.

Subjects were located and recruited using updated information from the CHDS birth cohort and KPMCP records. The flow of recruitment is described in detail in a flow chart from a previous publication from the DIBS (Brown et al., 2009). In summary, of the 71 cases, 3 were deceased, 15 were ineligible (lived out of the area, psychosis too severe to allow for testing, excluded medical conditions), 8 could not be contacted, and 19 refused participation. Hence, there were 26 cases of SSD. Complete data on neuropsychological performance and maternal G/R infection status were available on 25 SSD cases (13 with schizophrenia, 6 with schizoaffective disorder and 6 with other schizophrenia spectrum disorders). The cases in the DIBS sample were representative of the PDS sample with regard to diagnostic status, maternal age, maternal race, maternal education, parity, offspring sex, diagnostic distribution of schizophrenia spectrum disorders, and prevalence of infection (Table 1).

All subjects provided written informed consent. The study protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute, the Kaiser Foundation Research Institute, the University of California, San Francisco, and the San Francisco Department of Veterans Affairs Medical Center.

2.4. Neuropsychological assessments

Tests were administered by psychology doctoral students (minimum of master's level), trained by WSK and JP. In order to assess whether the findings were due to diminished global intelligence, full scale IQ was assessed by a WAIS-III short form. Based on the literature, our primary focus was on four neuropsychological domains: *Verbal memory* (California Verbal Learning Test); *Working memory* (Wechsler Adult Intelligence Scale [WAIS-III] Digit Span, Letter-Number Sequencing Test, Auditory N-back (2-back, 0-back) Tests); *Executive function* (Wisconsin Card Sorting Test [WCST], Trail Making Test Parts A and B [Trails A, Trails B]); *Verbal Fluency Test* [letter & category fluency], Ruff Figural Fluency Test [figural fluency]), and *Fine-motor coordination* (Grooved Pegboard Test, dominant hand). Processing speed was assessed with the Symbol Search and Digit Symbol tests. These tests have been described in detail elsewhere (Lezak et al., 2004).

2.5. Analytic method

We compared performance in each neuropsychological domain between SSD case offspring of mothers who were exposed and unexposed to maternal G/R infection. Unequal variances were found for certain response variables in the comparisons of exposed and unexposed cases. Consequently, analyses were performed with generalized linear models (GLM) (McCullagh and Nelder, 1989). GLM is a flexible parametric class of models suitable for small datasets in which the conditional distribution of the response given the predictors is selected from an exponential family (e.g., Gaussian, Poisson, binomial, gamma) and can capitalize on specific structure in the response variables of the study. The variance structure is determined by the particular GLM, with only the Gaussian model having constant variance. The canonical link function was used throughout. Binomial regression was utilized for the WCST, WAIS-III Digit Span Test, and Letter-Number Sequencing Test, with the number of test items determining the number of trials in the binomial model. For the Grooved Pegboard Test, the response is an event time, and a gamma regression model was used. For the Verbal Fluency Test and Ruff Figural Fluency Test, the outcome is number of correct responses, which has no predetermined upper-bound, and a Poisson regression model was applied. Finally, for the CVLT, Trails B Test, Auditory N-back Test, WAIS IQ tests, Symbol Search Test, and Digit Symbol Test, a Gaussian model was used.

To mitigate the potential for type I error due to multiple comparisons, composite scores consisting of sums of z-scores over tests in a given domain were examined using the Gaussian model (fine-motor coordination involved only one test). Statistical significance was initially assessed using $P < 0.05$; all tests were two-tailed. In addition, Bonferroni correction was applied; given 4 composite neuropsychological outcome measures, the corrected P was < 0.0125 . Given the small sample size, and the reduction of statistical

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