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PRENATAL INFECTION AND CAVUM SEPTUM PELLUCIDUM IN ADULT SCHIZOPHRENIA

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Abstract

Increased length of the cavum septum pellucidum (CSP) and *in utero* infection are each associated with increased risk of schizophrenia. Hence, we examined whether prenatal infections are related to CSP length in schizophrenia patients. In a well-characterized birth cohort, in utero infection was assessed using serologic biomarkers or physician diagnoses. Magnetic resonance images were acquired, and CSP length was quantified by a standard protocol. I*n utero* infection was associated with increased CSP length in exposed schizophrenia cases compared to unexposed cases, suggesting that prenatal infection plays a role in a neurodevelopmental morphologic anomaly that has been related previously to schizophrenia.

Keywords

schizophrenia; infection; virus; cavum; MRI; neurodevelopment

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Contributors

Alan S. Brown: Primarily responsible for designing the study, overseeing the statistical analysis, and manuscript writing.

Raymond F. Deicken, Sophia Vinogradov, William S. Kremen, John H. Poole and Catherine A. Schaefer: Contributed to study design, data collection, and manuscript writing.

Justin D. Penner, Anna Kochetkova, David Kern: Contributed to statistical analysis and manuscript writing.

All authors contributed to and have approved the final manuscript.

Conflict of Interest

None of the authors has any possible conflict of interest, financial or otherwise, related directly or indirectly to the submitted work.

1. Introduction

Accumulating evidence indicates that schizophrenia arises at least in part from a prenatal neurodevelopmental disruption. One of the most reliable markers of cerebral dysgenesis is cavum septum pellucidum (CSP), the compartment between the leaflets of the septum pellucidum that separates the ventricular frontal horns (Hopkins and Lewis 2000). In normal prenatal development, these leaflets fuse in a posterior to anterior direction, and this process is generally complete by six months of life (Farruggia and Babcock 1981). It has therefore been postulated that incomplete fusion of the septal leaflets, giving rise to CSP, could be secondary to an *in utero* or early postnatal insult.

Since a small CSP is generally considered to represent a normal variant, investigators have addressed whether CSP is larger in patients with schizophrenia compared to healthy controls (Degreef et al., 1992; DeLisi et al., 1993; Nopoulos et al., 1997; Kwon et al., 1998). Virtually all of these studies have reported larger CSP length in schizophrenia. These findings are consistent with a neurodevelopmental origin for this disorder. Yet, no previous study has examined specific *in utero* insults in relation to CSP.

Recent findings have implicated *in utero* exposure to infection in the etiology of schizophrenia (Brown et al., 2000; Buka et al., 2001; Brown et al., 2004; Brown et al., 2005; Babulas et al., 2006; Brown 2006; Mortensen et al., 2007). It is unclear, however, whether prenatal infection has neuromorphologic consequences that have been observed in schizophrenia. Hence, we examined the relationship between *in utero* exposure to several prenatal infections and CSP in patients with schizophrenia.

The subjects were derived from the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study. The study capitalized on infection data from analyses of prenatal archived sera and an extensive database on prospectively diagnosed *in utero* infections. These resources have been used in previous studies to demonstrate associations between prenatal infections and schizophrenia in this birth cohort (Brown et al., 2000; Brown et al., 2004; Brown et al., 2005; Babulas et al., 2006; Brown 2006).

2. Methods

2.1 Description of the cohort

The subjects were derived from the PDS study, which is elaborated in detail in a previous publication (Susser et al., 2000) and will therefore be only summarized. The mothers of the cohort members were enrolled from 1959–1966 in the Child Health and Development Study (CHDS), and nearly all gravidas received obstetric care from the Kaiser Permanente Medical Care Plan (KPMCP) in Alameda County, California.

The PDS sample consisted of the 12,094 live births who were KPMCP members from 1981–1997, corresponding to the period of case ascertainment. Maternal serum samples were collected during the pregnancies and were frozen and stored in a single repository. Subjects were classified with prenatal infection based on the presence of at least one of the following four infections that have been associated with schizophrenia in our previous work: early to mid-gestational influenza (Brown et al., 2004), elevated toxoplasma antibody (Brown et al., 2005), second trimester maternal respiratory infection (Brown et al., 2000), and periconceptional maternal/genital reproductive infection (Babulas et al., 2006). The methodology for exposure classification and analysis is described in full in previous publications, and is only briefly reviewed here (Brown et al., 2000; Brown et al., 2004; Brown et al., 2005; Babulas et al., 2006). Influenza and toxoplasma antibodies were identified by assays of prenatal sera. Prenatal influenza antibody was documented by hemagglutination

inhibition, following GLP standards (Gravenstein et al., 1994); influenza infection was defined as the first occurrence during pregnancy of an influenza antibody titer ≥20, and the timing of exposure was classified as influenza infection occurring from early to mid-gestation (day 0–142 post-LMP). Toxoplasma IgG antibody titers were determined by the screen agglutination test, followed by the Sabin-Feldman dye test (Montoya 2002), the reference standard. In accord with our previous finding (Brown et al., 2005), exposure was defined as a toxoplasma IgG antibody titer ≥1:128.

Second trimester maternal respiratory infection and periconceptional (genital/reproductive infection) were derived from extensive obstetric and medical records from the CHDS and KPMCP (Brown et al., 2000; Babulas et al., 2006). All second trimester (gestational days 91–180) acute respiratory infections in the CHDS dataset were included. Subjects were considered as exposed to respiratory infection if they had at least one of the following: tuberculosis, pneumonia, pleurisy, emphysema, viral respiratory infections, acute bronchitis, and upper respiratory infections. All periconceptional (30 days before the LMP until 30 days post-LMP) maternal genital/reproductive infections present in the database were included (Brown et al., 2000). Subjects were considered as exposed to genital/reproductive infection if they had at least one of the following: endometritis, cervicitis, pelvic inflammatory disease, vaginitis, syphilis, condylomata, “venereal disease,” and gonorrhea.

2.2 Ascertainment and diagnosis

The protocol for ascertainment and diagnosis of schizophrenia and other schizophrenia spectrum disorders (SSD) is fully described in a previous publication (Susser et al., 2000). Case ascertainment and screening were accomplished following computerized record linkage between the CHDS and KPMCP identifiers from inpatient, outpatient, and pharmacy registries. Potential cases were diagnosed by DSM-IV criteria following assessment with the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), chart review, and consensus of three experienced research psychiatrists based on the DIGS and psychiatric/medical records.

All cases and matched controls were targeted for neuroimaging assessments. We enrolled 21 cases of SSD, as previously defined (Susser et al., 2000), and 21 matched controls for MRI acquisition and analysis. Given that there were too few controls with prenatal infection to permit a meaningful analysis, the sample for the statistical analysis was restricted to cases only.

Among the 21 SSD cases, one had not undergone assays for prenatal influenza and toxoplasma, resulting in 20 cases, including 8 with schizophrenia, 6 with schizoaffective disorder, and 6 with other schizophrenia spectrum disorders. Among these, 12 cases were exposed to at least one of the specified infections and 8 were unexposed.

2.3 Image acquisition and analysis

MR images were acquired using a 1.5-Tesla Siemens system. Coronal T1-weighted images were obtained from 3D MP-RAGE sequences (TR/TI/TE=10/250/4 ms, resolution 1 × 1 mm^2, 1.4mm slice thickness). Measurements of CSP length (anterior to posterior) were made by identifying the number of contiguous coronal slices on which the CSP was observed and multiplying by the slice thickness, in accord with Nopoulos et al. (1997). The interoperator and intraoperator correlations were 0.96 and 0.99, respectively.

2.4 Statistical analysis

We utilized a continuous, rather than a categorical, measure of CSP length in order to maximize statistical power, given the modest sample size. The analysis consisted of linear regression with CSP length as the dependent variable and the indicator for exposed-unexposed status as

a predictor variable. Adjustment was made for intracranial volume and maternal ethnicity. Statistical significance was based on $p < .05$; all tests were two-tailed.

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

3. Results

There was a marked and statistically significant increase in mean (SD) length of the CSP in schizophrenia cases who were exposed to *in utero* infection [4.67 (3.65) mm] compared to cases who were unexposed to infection [1.75 (2.87) mm,], adjusting for intracranial volume and maternal ethnicity ($\beta = 3.26$, df =17, p=.049). For exposed cases, 11 of 12 (92%) had CSP lengths greater than 1.4 mm. For unexposed cases, 6 of 8 (75%) had CSP lengths of 1.4 mm or less. Mean (SD) CSP length in exposed versus unexposed controls were 4.2 (1.4) mm and 0.35 (0.7) mm, respectively, though these results were based on only 7 controls.

4. Discussion

We have demonstrated that prenatal infection is associated with significantly greater length of the CSP in schizophrenia cases. To our knowledge, this is the first systematic investigation of a known prenatal factor in relation to CSP. Controls exposed to prenatal infection, compared to unexposed controls, also evidenced an increase in CSP length, though this result must be considered as preliminary given the small number of controls.

Increased CSP length has been demonstrated in several previous studies of patients with schizophrenia, including first-episode (Kwon et al., 1998) and childhood-onset cases (Nopoulos et al., 1998). These findings have been interpreted as evidence of a midline developmental disruption during early life in schizophrenia, since the septal leaflets are believed to largely fuse by six months of age. Our study suggests that *in utero* infections that have been associated with schizophrenia in previous studies may play an etiologic role in the increased CSP length observed, and in the risk of schizophrenia.

CSP and other septum pellucidum abnormalities have been associated with numerous other neurodevelopmental conditions, including macro/microcephaly, mental retardation, and developmental delay (Schaefer et al., 1994). Prenatal infections have figured prominently in the etiology of these disorders (Bodensteiner et al., 1998), further enhancing the plausibility of the findings. Although the functional significance of enlarged CSP is unclear, investigators have hypothesized that this brain anomaly may be a marker of limbic system dysgenesis, particularly in the development of the hippocampus or corpus callosum.

5. Conclusion

We have demonstrated that *in utero* infection, derived from prospectively documented data in a well-characterized birth cohort, is associated with increased length of the cavum septum pellucidum. This finding suggests that *in utero* infection plays a role in a morphologic anomaly that is neurodevelopmental in origin and that has been related to schizophrenia in previous studies. Hence, the present study provides further evidence for prenatal infections in the etiopathogenesis of this disorder. Future studies with larger sample sizes are essential.

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