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Maternal serum cytokine levels and risk of bipolar disorder

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ABSTRACT

Prenatal exposure to influenza has previously been associated with increased risk of bipolar disorder (BD), an association that may be mediated by maternal cytokines. The objective of this study was to determine the association between maternal levels of cytokines measured during each trimester of pregnancy and the risk of BD in offspring. We conducted a case-control study nested in the Child Health and Development Study, a birth cohort that enrolled pregnant women in 1959–1966. Potential cases with DSM-IV-TR bipolar I disorder, bipolar II disorder, BD not otherwise specified, and BD with psychotic features were ascertained through electronic medical records, a public agency database, and a mailing to the cohort. Diagnoses were confirmed by clinical interview. Nine cytokines (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IFN-γ, TNF-α and GM-CSF) were measured simultaneously by Luminex assays in archived prenatal maternal serum samples from 85 cases and 170 matched controls. Data were analyzed using conditional logistic regression. In the overall study sample, there were no significant associations between prenatal maternal cytokine levels and BD after adjustment for confounders. The risk of BD without psychotic features was decreased among subjects with higher maternal levels of first trimester log-transformed IL-4 (OR (95% CI) = 0.76 (0.58, 0.98); p = 0.04) and third trimester log-transformed IL-6 (OR (95% CI) = 0.64 (0.42, 0.98); p = 0.04). In conclusion, higher levels of prenatal maternal cytokines were not associated with increased risk for BD. Further studies with larger samples are necessary to confirm the finding.

1. Introduction

Bipolar disorder (BD) is generally thought to result from a combination of genetic and non-genetic factors (Rush, 2003). The potential relevance of exposures occurring during the prenatal period is suggested by structural brain abnormalities associated with BD (Nasrallah, 1991) and by evidence that the risk of BD is increased among offspring of pregnancies affected by obstetric complications (Hultman et al., 1999; Kinney et al., 1993, 1998), pre-term birth (Nosarti et al., 2012), exposure to famine (Brown et al., 2000) and maternal smoking (Talati et al., 2013). Moreover, the overlap in clinical features and genetic risk factors between BD and schizophrenia (Lin and Mitchell, 2008; Purcell et al., 2009; Smoller et al., 2013) suggests that non-genetic risk factors may be shared as well. Prenatal exposure to maternal infection has been repeatedly identified as a risk factor for schizophrenia (reviewed in Brown, 2011). The findings that IL-8 was elevated during the second trimester among mothers of persons with schizophrenia (Brown et al., 2004) and that TNF-α and IL-8 were elevated in late pregnancy among mothers of those with psychosis (Buka et al., 2001) indicate that this association may be mediated through immune activation, including altered cytokine levels. Prenatal maternal immune activation has been demonstrated to disrupt neurodevelopment in animal models (reviewed in Patterson (2009)).

There have been relatively few studies on prenatal exposure to infection and BD (Brown, 2015). Recently, a clinical diagnosis of maternal influenza was associated with a nearly fourfold increased risk of BD in the Child Health and Development Study (CHDS) cohort Parboosing, 2013. Serologically documented maternal influenza was later found to confer a fivefold increased risk of BD with psychotic features, but not without psychotic features, in the same cohort (Canetta et al., 2014). Findings from other studies of influenza exposure that were not based on antibody measures in

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maternal sera have been mixed (Stober et al., 1997; Mortensen et al., 2011; Machon et al., 1997). To our knowledge, no previous studies have examined relationships between levels of maternal cytokines and BD.

To determine whether prospectively assayed prenatal maternal cytokine levels are associated with BD in the offspring, we measured 9 cytokines in archived maternal serum samples from different periods during pregnancy in BD cases and matched controls drawn from the CHDS cohort. We hypothesized that the pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and in particular IL-8, would be elevated in mothers of cases relative to controls. We further hypothesized that this association would be strongest in the second trimester and in BD cases with psychotic features.

2. Methods

2.1. Description of the cohort

Cases and controls were drawn from the Child Health and Development Study (CHDS) cohort van den Berg et al., 1988. Nearly all women receiving prenatal care from the Kaiser Permanente Medical Care Plan, Northern California Region (KPNC) in Alameda County, California from 1959 to 1966 (n = 19,044 live births) were recruited to the study. Extensive data were collected prospectively from sources including medical records and maternal interviews. Additionally, biospecimens were obtained and archived, including maternal serum samples from each trimester of pregnancy.

2.2. Case ascertainment and diagnosis

Ascertainment of BD cases has been described in depth elsewhere (Canetta et al., 2014), and is summarized here. Cases with DSM-IV-TR BD, including bipolar I disorder, bipolar II disorder, BD not otherwise specified, and BD with psychotic features, were identified through the following 3 sources: the KPNC electronic medical records database, the Alameda County Behavioral Health Care Services (ACBHCS) database, and a mailing to the entire living CHDS birth cohort (mothers and children).

KPNC inpatient (covering 1981–2010), outpatient (beginning in 1995), and outpatient pharmacy (beginning in 1992) databases were used to screen for CHDS subjects with potential BD and other psychotic disorders through computerized record linkages. Subjects were considered to have potential BD if they met either of the following criteria: inpatient discharge diagnoses of ICD-9 codes 295 through 298; outpatient diagnoses of ICD-9 codes 295 through 298, excluding unipolar major depressive disorder. Potential BD cases also included subjects treated with prescriptions for mood-stabilizing medications used in the treatment of BD (lithium carbonate, carbamazepine, and valproic acid). An additional means of identifying patients was by a mailing to all living cohort members (n = 13,009) and mothers (n = 6971) with known addresses who had not already been identified in one of the database sources; this was conducted in 2009–2011. The mailing included a questionnaire on mental and physical health, and those reporting "mental health problems" in a cohort member were administered the Family Interview for Genetic Studies. Subjects were considered to have potential BD if the interview indicated the presence of at least one bipolar or psychotic symptom.

Subjects with potential BD as identified above were invited to participate in a clinical interview. Of the 448 subjects with potential BD, 214 were interviewed by qualified, trained study interviewers using the Structured Clinical Interview for DSM-IV-TR (SCID-I/P). The subjects who did not complete an interview consisted of those who could not be contacted, refused to participate, did not keep an interview, or could not be interviewed. Diagnoses were assigned by a consensus of three experienced doctoral-level psychiatric clinicians. This resulted in a total of 72 diagnosed BD cases.

An additional 23 cases with BD identified through KPNC records by an earlier study (Prenatal Determinants of Schizophrenia Study (Susser et al., 2000) were also included. These cases were diagnosed using the Diagnostic Interview for Genetic Studies (DIGS) Nurnberger et al., 1994. This resulted in a total of 95 BD cases identified in the CHDS birth cohort. One of a pair of siblings with BD was excluded at random. For 85 of these 94 cases there was at least one maternal serum sample from pregnancy available with a sufficient quantity of serum for the analysis. These 85 cases were included in the present study. A schematic diagram of this ascertainment process can be found in Canetta et al. (2014).

2.3. Selection of matched controls

Controls were initially matched to all 95 confirmed BD cases in an 8:1 ratio. All CHDS cohort members who screened positive for potential BD or schizophrenia spectrum disorders (n = 448) were excluded as potential controls. Siblings of selected controls were also excluded, in order to maintain independence of observations. Matching criteria included: date of birth (±30 days), sex, gestational timing, the availability of archived maternal sera, and membership in KPNC (for cases ascertained through KPNC records) or residence in Alameda County (for cases ascertained through ACBHCS or CHDS mailing) in the year the case was first treated as reported in the SCID/DIGS. Siblings of selected controls were excluded from further control selection to ensure independence of observations. For each of the 85 cases with maternal serum samples available, the two matched controls most closely resembling the case with regard to timing of each serum draw were selected, for a total of 170 controls.

2.4. Measurement of cytokines in maternal serum samples

Serum samples were spun for 5 min at 10,000 rpm in a minicentrifuge. The supernatant was assayed for 9 cytokines (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IFN-γ, TNF-α and GM-CSF) in duplicate. All analytes were assayed simultaneously in a multiplex format using human high sensitivity cytokine/chemokine kits (Milliplex Map Kits, EMD Millipore Corporation, Billerica, MA) according to the manufacturer's instructions. In brief, samples were incubated overnight at 4 °C with a mixture of microspheres; each set of spheres is supplied with a single capture antibody specific for one of the analytes. Each microsphere is also internally coded with a unique mixture of fluorescent dyes. The 96 well filter plate was then washed twice by vacuum filtration, incubated for 1 h at room temperature with biotinylated detection antibodies, washed, and then incubated for 30 min at room temperature with streptavidin-phycoerythrin. Plates were read in a Luminex 100 Analyzer (Luminex, Austin, TX) controlled by STarStation 2.0 software (Applied Cytometry, Sheffield, UK). Two fluorescent signals were measured from individual beads; one identified the bead type and the other measured the fluorescent intensity of the bound phycoerythrin. Values for each analyte were determined from a standard curve of log dose versus median fluorescent intensity using a 5 parameter logistic fit.

2.5. Quality control

All samples were analyzed in duplicate, resulting in two measures per subject for each trimester-cytokine combination. Five samples were excluded for all cytokines because data from the duplicate was not available. In order to assess the reliability of the cytokine measurements, we calculated the coefficient of