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Low maternal hemoglobin during pregnancy and diminished neuromotor and neurocognitive performance in offspring with schizophrenia

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ABSTRACT

Objective: Previous research has linked maternal anemia during pregnancy with increased risk for schizophrenia in offspring. However, no study has sought to determine whether this early insult leads to a more severe form of the disorder, characterized by worsened motor and neurocognitive functioning.
Method: Subjects were 24 cases diagnosed with schizophrenia and 22 controls from the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study. Hemoglobin values were measured throughout pregnancy. Among offspring, psychiatric diagnoses were determined through semi-structured interviews and medical records review and comprehensive neurocognitive assessment batteries were conducted in adulthood.
Results: Results indicated that among cases decreases in maternal hemoglobin led to significant decreases in scores on the Grooved Pegboard test, the Finger Tapping test and the Wechsler Adult Intelligent Scales (WAIS) information subtest. In contrast, controls only exhibited decreases in performance on the California Verbal Learning Test (CVLT) long-delay recall after fetal exposure to lower hemoglobin. There were also significant interactions between hemoglobin and case status for all of the motor tasks.
Conclusions: These findings support the hypothesis that fetal exposure to decreases in maternal hemoglobin is related to preferentially poorer neuromotor function among cases compared to controls, as well as general intellectual difficulties among cases. Controls were relatively unaffected by decreased maternal hemoglobin, which suggests that liability to schizophrenia renders cases susceptible to the deleterious influences of in utero exposure to decreases in maternal hemoglobin.

1. Introduction

Neuromotor disruptions have been consistently associated with schizophrenia, with such difficulties occurring premorbidly (as early as infancy) and in neuroleptic naïve patients (Walker et al., 1994; Wolff and O'Driscoll, 1999; Pappa and Dazzan, 2009). In addition, cognitive difficulties have been repeatedly deemed to be a core characteristic of schizophrenia (Kuperberg and Heckers, 2000). Although there is variability among studies, the most commonly replicated cognitive deficits among schizophrenia patients have been in the areas of attention, information processing, working memory, executive functioning, language and memory (Kuperberg and Heckers, 2000; Barch, 2005). Further, cognitive and motor problems have been found in children prior to the onset of schizophrenia, suggesting that these difficulties may have developmental origins and are not entirely the result of the confounding influences of medication use and symptom onset (Rosso et al., 2000; Reichenberg et al., 2006). Nevertheless, it is unclear whether motor and cognitive problems associated with schizophrenia are related to genetic vulnerability for schizophrenia, environmental factors, or a combination of genetic and environmental influences.

Despite a presumed large genetic component to the causes of schizophrenia, concordance rates approximating 50% between monozygotic twins indicate the presence of a substantial environmental influence in the etiology of the disorder (Cannon et al., 1998). Among the

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potential environmental contributors, pre- and perinatal complications have been among the most well-documented risk factors associated with schizophrenia (Cannon et al., 2002). Although many obstetric events have been examined in schizophrenia research, in a previous investigation derived from the birth cohort of the current study, decreases in maternal mean hemoglobin (Hb) levels during pregnancy were linked to a significant increase in risk for schizophrenia in a dose–response fashion (Insel et al., 2008). Further, maternal anemia during pregnancy has been associated with obstetric complications (OCs) that have been linked to schizophrenia, such as fetal hypoxia, maternal malnutrition during pregnancy, and low birth weight (Viteri, 1994; Rasmussen, 2001; Cannon et al., 2002; Casanueva and Viteri, 2003). Despite these findings, no study has investigated whether fetal exposure to low maternal Hb during pregnancy is related to motor and cognitive difficulties among patients with schizophrenia.

The present study sought to determine whether fetal exposure to decreases in maternal Hb was related to diminished neuromotor and neurocognitive performance among cases with schizophrenia and other schizophrenia spectrum disorders (herein referred to as schizophrenia) and matched controls. Based on repeated findings in animal studies linking fetal exposure to maternal anemia to neuromotor problems, as well as learning and memory difficulties, we predicted that fetal exposure to decreases in maternal Hb would be related to poorer performance on motor tasks, as well as learning and memory tasks in adulthood (Jorgenson et al., 2003; Beard et al., 2006; Lozoff and Georgieff, 2006; Lozoff et al., 2006). For this purpose, we conducted analyses of hemoglobin and neuromotor/neurocognitive performance separately in cases and controls. Further, it was hypothesized that cases, compared to controls, would be preferentially sensitive to decreases in maternal Hb with regard to function on these tests, consistent with previous studies examining the influences of hypoxia-associated OCs in schizophrenia populations (van Erp et al., 2002; Cannon et al., 2008). Hence, we also examined whether there was an interaction between case/control status and Hb in relation to neuromotor/neurocognitive performance. These latter analyses were considered to be exploratory associations, due to reduced power for testing interactions. Exploratory analyses also were conducted on measures of attention, working memory, and executive functioning due to the relationship between these cognitive domains and schizophrenia (Kuperberg and Heckers, 2000; Barch, 2005).

2. Materials and methods

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

2.1. Description of the cohort

The subjects were derived from the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study, which was based on participants from the Prenatal Determinants of Schizophrenia (PDS) study. The PDS study was a follow-up of a large birth cohort to determine who among the offspring developed schizophrenia, described in detail in a previous publication (Susser et al., 2000). Briefly, the PDS study included pregnant women (N = 12,094 live births) receiving obstetric care from the Kaiser Permanente Medical Care Plan (KPMCP) in Alameda County, California, as part of the Child Health and Development Study (CHDS). Maternal Hb data were available for 6872 of 7791 mothers of the PDS Cohort (88.2%), which were extracted from detailed prenatal medical records.

2.2. Ascertainment and diagnosis

The protocol for ascertainment and diagnosis of schizophrenia cases is described in detail in a previous publication (Susser et al., 2000). Computerized record linkage between the CHDS and KPMCP identifiers from inpatient, outpatient, and pharmacy registries was conducted to ascertain schizophrenia cases from the CHDS cohort. Ascertained cases consisted of cohort members who belonged to KPMCP from 1981 to 1997. 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 3 experienced research psychiatrists based on the DIGS and psychiatric/medical records. Comparison subjects were matched 1:1 to the case subjects on membership in KPMCP at the time of case ascertainment, date of birth, sex, and availability of maternal sera (reviewed in Brown et al., 2009).

All cases were targeted for neuropsychological assessment. Twenty-six cases and 24 controls completed neuropsychological assessments and of these participants, 24 cases and 22 controls had available mean Hb data from their mothers' pregnancies. As Table 1 indicates, there were no significant differences between cases and controls on a variety of demographic characteristics.

2.3. Hemoglobin assessment

Hb is a protein found in red blood cells, which carries oxygen from the lungs to peripheral tissues and is decreased with anemia (Bunn and Poyton, 1996). Hb is an excellent indicator of iron status and blood oxygenation (Bunn and Poyton, 1996; Tam and Lao, 1999). Maternal Hb concentrations from blood samples collected throughout pregnancy were extracted from obstetric records. Hb values were available from 14 subjects (7 cases) in the first trimester, from 34 subjects (18 cases) in the second trimester, and from all subjects in the third trimester. To maximize power, and in accord with the previous association between mean prenatal Hb levels and risk for schizophrenia, mean Hb levels throughout pregnancy were used in the present study (Insel et al., 2008). The majority of subjects (17

Table 1
Demographic characteristics of the samples (Means, standard deviations, frequencies, and percentages).

Characteristic	Schizophrenia cases (n = 24)	Control subjects (n = 22)	p-Value
Female offspring	25.00%	31.82%	0.608
Age of offspring at testing	39.77 (1.83)	40.87 (1.91)	0.052
Birth weight (grams)	3451.61 (611.44)	3246.08 (569.74)	0.246
Gestational age (weeks)	40.66 (1.89)	39.78(1.59)	0.103
Maternal age	28.29(6.52)	28.23 (5.85)	0.972
# of previous deliveries	2.00 (2.14)	1.27 (1.28)	0.172
Maternal education			
(≥HS grad)	65.22%	54.55%	0.465
Maternal race			
Caucasian	12 (50%)	12 (54.55%)	0.725
African American	10 (41.67%)	7 (31.82%)	
Other	2 (8.33%)	3 (13.64%)	
Hemoglobin (g/dL)	10.871 (0.84)	11.327 (1.20)	0.138
Medication use			
Atypical antipsychotics[a]	8 (33.33%)	0	0.003
Typical antipsychotics	5 (20.83%)	0	0.023
Any antipsychotic	10 (41.67%)	0	0.0006
Anti-pyramidal medications	5 (20.83%)	0	0.023
Mood stabilizers	6 (25.00%)	0	0.012
SSRIs	3 (12.50%)	0	0.086
Ritalin	1 (4.17%)	0	0.333
Vicodin	0	1 (4.55%)	0.291
Benzodiazepines	1 (4.17%)	0	0.333

HS = high school; g/dL = grams per deciliter.
[a] 1 subject was taking Clozaril.