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Research Report

Perinatal oxytocin increases the risk of offspring bipolar disorder and childhood cognitive impairment

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ABSTRACT

Background: We tested the hypothesis that perinatal oxytocin, given to pregnant women to induce labor, is related to offspring bipolar disorder (BP) and worse childhood cognitive performance among offspring. We also tested the association between childhood cognition and later BP.
Methods: A population-based birth cohort derived from the Child Health and Development Study (CHDS) which included nearly all pregnant women receiving obstetric care from the Kaiser Permanente Medical Care Plan, Northern California Region (KPNC) between 1959 and 1966. Prospectively obtained medical and offspring cognitive performance were used. Potential cases with BP from the cohort were identified by database linkages. This protocol identified 94 cases who were matched 1:8 to controls.
Results: Perinatal oxytocin was associated with a 2.4 times increased odds of later BP. Oxytocin was also associated with decreased performance on the Raven Matrices, but not on the Peabody Picture Vocabulary Test (PPVT). Childhood cognition was not associated with later BP.
Limitations: Loss to follow-up must be considered in all birth cohort studies. In addition, the childhood cognitive battery did not include tests related to multiple domains of cognition which have been associated with later BP. A third limitation is the modest sample size of those exposed to oxytocin.
Conclusions: This study provides evidence for a potentially important perinatal risk factor for BP and cognitive impairment in childhood. While the association between perinatal oxytocin and offspring BP must be viewed cautiously until further studies can attempt to replicate the result, it lends support to the broader view that neurodevelopmental factors contribute to BP.

1. Introduction

Bipolar disorder (BP) has been thought to be related to schizophrenia (SZ) in certain respects, and as the neurodevelopmental hypothesis of SZ has become increasingly accepted, a similar hypothesis has been applied to BP (Bearden et al., 2001; Demjaha et al., 2012; Goodwin et al., 2008; Murray et al., 2004; Quraishi and Frangou, 2002; Sanches et al., 2008; Tamminga et al., 2013). The neurodevelopmental hypothesis posits that altered, pathological, or delayed maturation of the developing brain shifts the neurodevelopmental trajectory, followed by later onset of psychiatric illness (Fish et al., 1965; Meyer and Feldon, 2010; Millan, 2013; Murray and Lewis, 1987; Nasrallah and Weinberger, 1986; Oneal and Robins, 1958). Currently, evidence supporting the neurodevelopmental hypothesis of BP is less robust than the evidence supporting the corresponding hypothesis for SZ.

For instance, cognitive impairment during the premorbid and prodromal phases appears to be milder in BP compared with SZ (Seidman et al., 2013; Urfer-Parnas et al., 2010; Zanelli et al., 2010). Population based conscript studies have reported small but significant differences in overall premorbid cognitive performance in BP (Osler et al., 2007; Sorensen et al., 2012; Tiihonen et al., 2005; Urfer-Parnas et al., 2010), although some other studies have found better than average cognition (MacCabe et al., 2013). A review of longitudinal, family, and first episode neuropsychological studies found that domain specific functions (executive and memory) are consistently impaired in those who later develop BP (Olvet et al., 2013). However, a review of population based studies concluded that the evidence is not sufficient to determine whether premorbid cognitive impairment is a trait of later BP (Kravariti et al., 2009). In addition, fewer prenatal and perinatal exposures have been found to be associated with BP compared with SZ, though

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this may be because fewer studies have been performed (Sanches et al., 2008; Tsuchiya et al., 2003).

The neurodevelopmental approach to the origin and course of SZ and BP holds promise for improving outcomes because it searches for the causes and mechanisms which result in illness later in life, opening the potential for earlier and more effective intervention and prevention. As suggested by Insel, the neurodevelopmental approach identifies stages of disease progression, each of which may offer specific types of intervention and preventive strategies (Insel, 2010).

The rate of inducing labor has increased in recent decades, with oxytocin now being the most commonly used intervention (Mealing et al., 2009; Moleti, 2009). However, perinatal exogenous oxytocin has been associated with health risks for the neonate (Buchanan et al., 2012). These include lower Apgar scores and a greater need for neonatal intensive care (Oscarsson et al., 2006; Selo-Ojeme et al., 2011); and worse infant prefeeding behaviors immediately following birth (Bell et al., 2013). As observed in clinical studies of adults, and consistent with animal models, oxytocin is associated with affective regulation and mood disorders (Demitrack and Gold, 1988; Lucht et al., 2009; Scantamburlo et al., 2007). In animal models, postnatal administration of oxytocin results in long-term maladaptive behavior and dysregulation of the HPA axis, as well as impairment in social and cognitive function (Carter, 2003; Engelmann et al., 1996; Rault et al., 2013). In clinical studies of healthy adults, oxytocin is associated with alterations in a number of cognitive domains including worse learning, attention, memory, and adaptive behaviors, but also with improving social and affiliative behaviors (Cardoso et al., 2014; Demitrack and Gold, 1988; Ellenbogen et al., 2012; Herzmann et al., 2012; Lerer et al., 2008).

Although oxytocin is associated with neurodevelopmental illnesses (Gregory et al., 2013; Kurth and Haussmann, 2011), no previous studies have examined the association of exogenous perinatal oxytocin and the risk of BP. In addition, while some obstetric complications have been associated with childhood cognitive deficits (Leitner et al., 2007; Seidman et al., 2000), no studies of maternally administered exogenous oxytocin in relation to cognitive performance in childhood have been conducted.

Perinatal oxytocin to induce labor, therefore, merits further investigation for its association with BP and cognitive impairment, given the possible mechanisms by which it alters neurophysiology and its use during birth when the developing brain is at increased risk. The Child Health and Development Study (CHDS) is a large, representative birth cohort and the current nested case–control study identified BP cases and matched controls to assess prenatal and perinatal risks for later onset BP by longitudinal follow-up. In this study, we tested the following hypotheses: 1) the offspring of mothers who received oxytocin to induce labor are at greater risk for later BP; 2) the offspring of mothers who received oxytocin perform worse on childhood cognitive testing; and 3) predicated on substantiating the first two hypotheses, cognitive performance mediates the association between oxytocin and BP.

Secondary analyses were also conducted to attempt to determine whether gestational age, prolonged labor, analgesics, or delivery type confounded the relationship between oxytocin and BP. Gestational age and prolonged labor could each share a common cause with perinatal oxytocin induction if the pregnancy or labor is longer than expected, or could be antecedents leading to oxytocin administration. Analgesics during labor, reflecting the possibility that any medication intervention could alter the risk for later illness, and delivery type, which may indicate conditions of labor progress, could also confound or mediate an association between oxytocin and BP.

2. Methods

BP cases and matched controls were drawn from the Child Health and Development Study (CHDS) birth cohort. The CHDS recruited nearly all pregnant women receiving obstetric care ($N=19{,}004$) from the Kaiser Permanente Medical Care Plan, Northern California Region (KPNC) in Alameda County, California between 1959 and 1966 and followed them prospectively (van den Berg et al., 1988). Comprehensive data were collected from maternal medical records and interviews, child assessments, and other sources. KPNC enrolled approximately 30% of the population of the Bay Area of California at the time. This birth cohort has been extensively studied for prenatal and other early developmental risk factors for SZ (Brown et al., 2004, 2005, 2009; Freedman et al., 2011; Perrin et al., 2007).

2.1. Case identification

Subjects with potential DSM-IV BP, which included BP I, BP II, BP NOS, and BP with psychotic features, were ascertained from three sources: the KPNC electronic medical records database, the Alameda County Behavioral Health Care Services (ABHCS) database, and a mailed survey to the entire living CHDS birth cohort (mothers and children). All CHDS cohort members who belonged to KPNC when first treated would have been ascertained from this source. Subjects who left KPNC prior to the first treatment of BP and who did not have other health insurance, but who still lived in Alameda County, would likely have been treated by ABHCS, and therefore ascertained. Subjects who were not ascertained by these two approaches were identified by the mailed survey.

The ascertainment process identified 448 subjects who potentially met the criteria for BP and/or other psychotic disorders.

2.2. Ascertainment of KPNC subjects

Subjects with potential BP (and other psychotic disorders) were identified by screening KPNC inpatient and outpatient databases. Computerized record linkages between CHDS and KPNC identifiers were conducted on these databases. The inpatient database included all psychiatric hospitalizations of KPNC members regardless of the hospital at which treatment is received. This covered the period from 1981 to 2010. Those with discharge diagnoses of ICD-9 295–298 were considered as potential BP subjects. A database of outpatient treatment was introduced in 1981, but did not contain searchable codes for diagnoses until 1995. Potential BP cases from the outpatient database were considered potential cases if they received ICD-9 diagnoses of 295–298 excluding unipolar major depressive disorder. The outpatient pharmacy database, which commenced in 1992 was also used, with potential cases identified from prescriptions for mood stabilizing medications (lithium, carbamazepine, and valproic acid). For subjects enrolled in KPNC at the time of ascertainment, the subject's treating psychiatrist was contacted, informed about the study, and asked to approve contact with the subject to seek his/her consent to participate.

Subjects identified by these methods were invited to participate in the study, receiving a letter to the most recent address. Those who did not refuse contact by returning a postcard were contacted to arrange a diagnostic interview. Several repeat appointments were scheduled for subjects who failed to attend the interview. Extensive efforts were made to locate individuals who were no longer living at the most recent listed address, including Department of Motor Vehicles (DMV) records, telephone directories, and contacting the subjects' parents or siblings from CHDS or KPNC files. Mortality records, reverse directories, jail