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Reduced maternal levels of common viruses during pregnancy predict offspring psychosis: Potential role of enhanced maternal immune activity?

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ABSTRACT

Viral infections during the prenatal or early childhood periods are one of the environmental factors which might play an etiological role in psychoses. Several studies report higher antibody levels against viruses during pregnancy in blood of mothers of offspring with psychotic disorders, but the presence of such viruses has never been demonstrated.
The goal of this study was to investigate the potential association between viral infections during pregnancy and progeny with psychotic disorders and, for this purpose, we performed a nested case–control study involving pregnant mothers of offspring with schizophrenia or bipolar disorder with psychotic features (cases, N = 43) and pregnant women with healthy offspring (controls, N = 95). Since several potential viral candidates have been suggested in prior work, a broad-spectrum virus detection system was necessary.
A metagenomic analysis performed with the virus discovery method VIDISCA-454 revealed only common blood-associated viruses in all cohorts. However, a significantly lower viral prevalence was detected in the group of cases and in the sub-population of pregnant mothers of offspring with schizophrenia ($p < 0.05$). Consistent with the existing inverse correlation between the level of these viruses and the immunocompetence of an individual, we hypothesized the presence of a higher immune activity during pregnancy in mothers whose offspring later develop a psychotic disorder as compared to controls.
Combining our results with previously available literature data on antibody levels during the gestation period suggests that a more prominent maternal immune activity can be considered a risk factor for developing psychosis.

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1. Introduction

Several lines of evidence suggest that schizophrenia and bipolar disorder (BD) with psychotic symptoms are similar on a number of genetic and neurobiological characteristics and that psychotic symptoms may share a common etiology (Maier et al., 2006). Both disorders are regulated by a complex interaction of multiple genetic elements in concert with environmental factors and the overlap of clinical features might

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be a consequence of common pathophysiological pathways (Tsuang, 2000; Maier et al., 2006). Recent studies reported a positive correlation between exposure to infections during the vulnerable period of gestation and the risk of developing psychoses (Buka et al., 2001a; Buka et al., 2008; Blomström et al., 2012). This hypothesis is supported by the evidence of an increased risk for schizophrenia among offspring of pregnant mothers with higher antibody levels against several pathogens (Brown et al., 2001, 2004a, 2005). Elevated levels of maternal antibodies against viruses have also been found to be associated with BD with psychotic features among offspring (S.E. Canetta et al., 2014).

However, the serological evidence has not yet been followed by direct virological evidence since no pathogen transmittable to the fetus via the placenta has thus far been detected during pregnancy in blood of mothers of offspring with the above-mentioned psychotic disorders. Here, we investigated whether maternal viremia, specific to one or a set of viruses, was associated with psychoses (schizophrenia and BD) in the offspring using a blinded, nested, case–control study.

Since a wide variety of agents have been correlated with the disorder and the involvement of an unexpected or unknown virus could not be excluded, the use of a broad spectrum approach for virus determination was necessary. Sequence independent virus identification techniques allow the simultaneous molecular detection of multiple viruses from a clinical sample without requiring any prior knowledge of its virological composition, and the possibility of combining them with next generation sequencing confers to these methods high efficiency and sensitivity (Delwart, 2007). One of these methods is VIDISCA-454, a restriction enzyme based virus discovery technique which is able to detect virtually any DNA or RNA virus from clinical samples (De Vries et al., 2011, 2012) and which was successfully used for virus discovery and metagenomic studies (Canuti et al., 2011, 2014a,b; Jazaeri Farsani et al., 2013, 2015; Oude Munnink et al., 2014, 2013). For this work VIDISCA-454 was applied on sera collected from pregnant mothers of offspring with or without schizophrenia or BD with psychotic features to evaluate the hypotheses of a viral etiology of psychoses.

2. Materials and methods

2.1. Sample collection

Participants were selected from 17,741 pregnancies enrolled between 1959 and 1966 into the Boston and Providence sites of the Collaborative Perinatal Project [CPP] (Niswander and Gordon, 1972) also known as the New England Family Study (NEFS) (Goldstein et al., 2010, 2011; Seidman et al., 2013). The pregnant women ascertained in the CPP were largely representative of the patients receiving prenatal care at each participating center. Maternal serum samples were collected approximately every two months throughout pregnancy and stored at −20 °C. In a series of studies, we identified offspring participants who had developed schizophrenia and other psychotic disorders by adulthood (Goldstein et al., 2010, 2011; Seidman et al., 2013). Briefly, subjects were located through a variety of methods, including address directories, death certificates, motor vehicle reports, home visits, and/or record linkages with public hospitals, mental health clinics, and the Massachusetts and Rhode Island Departments of Mental Health. Systematic diagnostic interviews using the Structural Clinical Interview for Diagnosis (SCID [DSM-IV]) (First et al., 1996) and family history of psychiatric disorders using the Family Interview for Genetic Studies (Maxwell, 1996) were conducted by trained masters-level clinical interviewers and expert diagnosticians assessed Axis I diagnoses of any form of psychotic, major affective, bipolar or substance abuse or dependence disorders. Seventy-four were determined to have a DSM-IV diagnosis of schizophrenia or bipolar disorder (BD) with psychotic features. Of these we included 43 subjects with a diagnosis of schizophrenia (n = 31) or bipolar disorder (BD) with psychotic features (n = 12) for whom a third trimester sample was readily available.

The primary set of controls was selected from families participating in a larger study with no history of major psychiatric disorders (Goldstein et al., 2010, 2011), to account for the possible influence of genetically determined factors on the immune response against viral infections. Controls were NEFS adult offspring for whom parents and grandparents, as well as the parents' siblings, were free of any known lifetime history of psychosis, bipolar, schizotypal, recurrent major depressive disorder, suicide attempts, or psychiatric hospitalizations, as described previously (Goldstein et al., 2010). Siblings of the controls were also free of any lifetime history of psychosis or bipolar disorder. From the pool of 186 potential controls (Goldstein et al., 2014), we selected 43 controls matched, as best as possible, for season of birth, maternal race/ethnicity and level of education, and child gender. Approximately six months prior to the blind matched case–control assays, we investigated a set of 52 maternal control serum samples from this same population to ascertain that the method was suitable to detect viruses in such old samples. These mothers, none of which had documented schizophrenia or other psychotic disorders, were included in the following analysis as additional controls.

Human subjects' approval was granted by Harvard University, Brown University, Partners Healthcare system, and local psychiatric facilities. Written consent was obtained from all interviewed study participants, and subjects were compensated for participating.

2.2. Virus discovery: VIDISCA-454

To evaluate whether a virus (or a set of viruses) could be identified in association with the development of psychoses (schizophrenia and BD) a sequence independent virus discovery technique was used to perform viral metagenomics in serum samples collected from pregnant mothers of offspring with or without psychoses. Sample processing and sequence analysis were performed blindly.

VIDISCA-454 (Virus Discovery cDNA-AFLP) is a virus discovery technique that, combined with Roche 454 next generation sequencing, is able to detect virtually all DNA or RNA viruses from various clinical samples (Canuti et al., 2011, 2014a,b; Jazaeri Farsani et al., 2013, 2015; Oude Munnink et al., 2013, 2014; Tan et al., 2013; Pariani et al., 2014; Shaukat et al., 2014). Since this method is specifically designed to detect extracellular genetic material which is not susceptible to nucleases (viral genomes protected by a protein capsid), this system cannot be used to detect other human pathogens, such as bacteria and parasites.

Serum samples were tested as previously described with minor modifications (de Vries et al., 2011). Briefly, 110 μl of each sample was spun down to remove intact cells and 100 μl of supernatant was treated to eliminate background cellular DNA with 20 U TURBO™ DNase (Ambion). Nucleic acids were isolated as described by Boom et al. (1990). To subsequently detect RNA viruses a reverse transcription was performed with 200 U of Superscript II (Invitrogen) and non-ribosomal hexamers (Endoh et al., 2005), followed by a second strand synthesis with 5 U of Klenow fragment (3′–5′ exo-) (New England Biolabs) and 7.5 U of RNase H (New England Biolabs). After purification by phenol chloroform-extraction and ethanol precipitation, the obtained double stranded DNA was digested with 10 U of *MseI* (New England Biolabs) restriction enzyme. The A- and B-adaptors with multiplex identifiers, which contain specific Roche-454 primer binding sequences, were ligated to the digested fragments. After adaptor ligation, an amplicon size-selection was performed to prevent the amplification of DNA fragments smaller than 200 bp using Agencourt AMPure XP beads (Beckman Coulter), followed by 30 cycles of PCR amplification. The amplified library was then subjected to 2 consecutive purification rounds with Agencourt AMPure XP beads to completely remove excess primers and short fragments and DNA concentration was measured on a Qubit Fluorometer (Quant-it dsDNA HS Kit, Invitrogen). The libraries were pooled (35 samples per pool) and the average size of every pool was estimated with an Agilent 2100 Bioanalyzer (high sensitivity DNA Kit, Agilent Technologies) and the final concentration (copies/μl) was

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