New Serological Evidence Points Toward an Infectious Route to Bipolar Disorder

The exploration of possible immune mechanisms in mental illness is a long-standing area of research that continues to attract attention from basic researchers and clinicians alike. Within this neuro-immune framework of neuropsychiatric disease, a great deal of interest has been centered on the possible contribution of infections in prenatal life. The antenatal period is highly sensitive to the damaging effects induced by environmental insults such as infections, and thus considerable efforts have been made to delineate the role of prenatal infection in neuropsychiatric and neurological disorders with developmental components (1). Epidemiological research over the last four decades has provided accumulating evidence to support the hypothesis that prenatal exposure to infection or associated inflammatory processes can increase the risk of schizophrenia, which is characterized to a considerable extent by psychotic episodes (2). Psychotic symptoms are also frequent in bipolar disorder, a neuropsychiatric condition that appears to share a number of genetic and environmental risk factors with schizophrenia (3). The presence of apparent etiological and pathogenic similarities between schizophrenia and bipolar disorder has encouraged epidemiologists to address the question of whether prenatal exposure to infection may, similarly to schizophrenia, play a role in the development of bipolar disorder. However, studies of this kind are relatively rare and have thus far provided equivocal results (4, 5).

It is becoming increasingly evident that prenatal exposure to infection likely plays a role in the etiology of various neuropsychiatric and neurological disorders.

In this issue, Canetta et al. (6) present an important piece of evidence suggesting that maternal infection during pregnancy is indeed an early-life environmental risk factor of bipolar disorder. The authors used a nested case-control design in the Child Health and Development Study birth cohort, which included offspring of pregnant women who received obstetric care from the Kaiser Permanente Medical Care Plan in the northern California region and were born between 1959 and 1966 (7). This cohort is unique in that it contains maternal serum samples that were collected prospectively from pregnant women at each trimester and archived for subsequent serological testing. Canetta et al. (6) used this excellent opportunity to verify maternal influenza exposure during pregnancy in an attempt to identify a possible association between serologically documented influenza infection and risk of bipolar disorder in the offspring. The study included 85 diagnostically assessed bipolar disorder cases, which were identified according to longitudinal follow-up screening procedures in three database sources, namely the Kaiser electronic database, the Alameda County Behavioral Health Care Services database, and a follow-up mailed questionnaire. Thirty-six cases had psychotic features and 49 did not, and the 85 case subjects were matched to 170 comparison subjects.

Canetta et al. (6) report that maternal gestational exposure to influenza does not generally increase the risk of bipolar disorder in the offspring; they found no increased risk of bipolar disorder among offspring of influenza-exposed mothers when the entire bipolar disorder population was considered. Intriguingly, however, maternal influenza exposure during pregnancy was associated with a fivefold increased risk of bipolar disorder with psychotic features, but no significant association between maternal influenza exposure and bipolar disorder without psychotic features. The association between maternal influenza and bipolar disorder with psychotic features remained significant after controlling for potential confounding factors such as maternal race and after applying the Bonferroni correction to adjust for multiple comparisons. Additional analyses indicated that first and second trimester influenza infections may be more critical than third trimester infections. However, none of the trimester-specific associations attained statistical significance, possibly because of the limited sample size after stratification according to trimesters.

Although a significant association between maternal influenza infection and increased risk of bipolar disorder (with psychotic episodes) in the offspring has been previously documented (5), this latest study by Canetta et al. is the first to provide direct serological evidence for such an association. Immunological verification of infectious exposures is highly essential in developmental epidemiology. Indeed, attempts to link major neuropsychiatric disorders with prenatal environmental adversities such as maternal influenza exposure have often been met with criticism, partly because the findings provided by previous retrospective ecological studies were not always reproducible (2, 8, 9). Such retrospective epidemiological studies also lack a direct assessment of infectious exposure in the population studied, which therefore may lead to spurious findings. The Canetta et al. study is arguably less prone to such limitations because a specific infectious pathogen was available for serological verification and used for subsequent correlative analyses in the offspring years later. Such designs are very powerful approaches in developmental epidemiological research, and it is likely that they will further advance our understanding of how prenatal environmental insults like infection can contribute to neuropathological and psychopathological long-term outcomes associated with bipolar disorder. We have already seen such advances in the schizophrenia epidemiology field, in which associations between maternal infection and increased schizophrenia risk were confirmed by several prospective studies that involved immunological ascertainment of immune exposures (10–12).

One intriguing finding by Canetta et al. was that prenatal exposure to influenza increases the risk of bipolar disorder with psychotic features, but not of bipolar disorder without psychotic features. The authors note that this distinction may support the hypothesis that maternal influenza exposure could preferentially increase the risk of psychosis apart from traditional diagnostic categories (6). This notion would indeed be consistent with the previously identified associations between prenatal influenza exposure and schizophrenia (2, 10–12), a disorder characterized in large part by psychotic episodes. Additional support for this hypothesis stems from experimental research in animals showing altered development and functions of the central dopamine system, which in turn are strongly implicated in psychotic disease (13).

The distinction between infection-associated bipolar disorder with and without psychotic features adds to the ongoing debate of whether prenatal adversities such as infection are specific in terms of their neurodevelopmental and psychopathological

sequelae. Which neuropsychiatric diseases, if any, are most strongly associated with prenatal immune adversities such as maternal infection? With advances in epidemiological research, it is becoming increasingly evident that prenatal exposure to infection likely plays a role in the etiology of various neuropsychiatric and neurological disorders, including schizophrenia (2, 10–12), autism (14), bipolar disorder (5, 6), mental retardation (15), and cerebral palsy (16). Hence, prenatal exposure to infection may be best viewed as a general vulnerability factor for neurodevelopmental brain disorders rather than a disease-specific risk factor (17), and therefore, significant associations between maternal infection during pregnancy and increased disease risk in the offspring are being revealed even for seemingly remote brain disorders. The adverse effects induced by prenatal infection may reflect an early entry into developmental brain disorders, but the specificity of subsequent disease or symptoms is likely to be influenced by the genetic and environmental context in which the prenatal infectious process occurs (18, 19).

These considerations may also have important clinical implications because prevention of maternal infection during pregnancy may be effective in reducing a wide spectrum of neuropsychiatric and neurological disorders. Vaccination has become a mainstay for the prevention of influenza in general, and its prophylactic application to pregnant women is recommended by several health organizations (20). Ideally, influenza vaccination should be induced during preconception in order to fully avoid any negative perinatal outcomes associated with (transient) immune activation during pregnancy. It needs to be noted, however, that maternal vaccination during pregnancy appears safe and has not been associated with any fetal or neonatal complications (20–22). Given that prenatal exposure to influenza infection is now being established as a risk factor for several neuropsychiatric and neurological disorders, vaccination-based preventive approaches may indeed hold promise for reducing the incidence of neuronal maldevelopment in response to maternal infection.

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