Prenatal Risk Factors in Schizophrenia

January 01, 1996 | Schizophrenia [1], Schizophrenia Psychotic Features [2], Addiction [3]
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Significant research developments in the etiopathogenesis of schizophrenia have occurred during the past several years. One such advance is the "neurodevelopmental" hypothesis that events during early brain development, especially the prenatal and perinatal periods, may play an important causal role in at least some, and perhaps many, cases of schizophrenia.

Converging lines of evidence in favor of the neurodevelopmental hypothesis of schizophrenia derive largely from three areas of schizophrenia research: brain imaging/neuro-pathology, premorbid abnormalities and minor physical anomalies.

Brain imaging and cytoarchitectonic studies have consistently demonstrated increased ventricular size and reduced volumes of medial temporal lobe structures, and abnormalities of neuronal number and organization in patients with schizophrenia (Waddington 1993a,b; Suddath and others; Bogerts and others; Akbarian and others). The fact that structural brain anomalies occur in "first episode" patients suggests that they are likely present before the onset of illness (Waddington 1993a). In addition, children destined to develop schizophrenia have increased neuromotor and psychosocial abnormalities, including social withdrawal, disruptive behavior and emotional lability (Walker and others; Jones and others). The third piece of evidence derives from studies of minor physical anomalies (MPAs), minor malformations of the head, eyes, ears, hands, mouth or feet that are ectodermal in origin, and that are thought to result from environmental or genetic insults in the first or second trimesters (Green and others). Investigations of MPAs are of relevance to schizophrenia, since ectodermal development closely parallels maturation of the fetal brain, and patients with schizophrenia, compared to controls, have an increased occurrence of MPAs (Green and others).

The study of monozygotic (MZ) twins; discordant for schizophrenia has provided a critically important strategy to differentiate the relative contribution of genes and environment to adverse neurodevelopmental events. Because identical twins share all of their genes, any between-twin differences are presumed to be environmental in origin. In a landmark MRI study of discordant MZ twins, Suddath and colleagues demonstrated that almost every affected twin had increased ventricular size and diminished volumes of temporolimbic structures, including the hippocampus, compared to his or her respective unaffected twin. Further studies of discordant MZ twins, including investigations using positron emission tomography (PET) and dermal ridge counts (Bracha and colleagues), have provided additional evidence supporting environmental etiologies.

Although many different types of prenatal exposures are potential risk factors for schizophrenia, we shall focus upon three of the best studied: prenatal infection, prenatal nutritional deficiency and obstetric complications.

Prenatal infection.

It is well-known that many infectious agents have detrimental effects on fetal brain development. These infectious teratogens include rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV) (Whitley and Stagno). With respect to developmental pathology, several concordant findings exist between congenital infection syndromes resulting from these viruses and schizophrenia, including brain and dermatoglyphic abnormalities.
Many epidemiologic studies support a potential role for prenatal viral insults in schizophrenia. One of the first major pieces of evidence is the consistent demonstration of a 5 percent to 15 percent excess of births in the winter and early spring among individuals destined to develop schizophrenia (Torrey and Kaufmann). These findings led to a flurry of investigations attempting to relate epidemics of specific viral agents to the births of preschizophrenic patients.

Since influenza epidemics typically occur periodically in the winter and affect a significant proportion of the population, most epidemiologic studies of prenatal infection and schizophrenia have focused on this virus. Several of these studies do suggest that prenatal influenza exposure is a risk factor for schizophrenia. The 1957 type A2 influenza epidemic, the second most severe pandemic of this century, provided investigators with an excellent opportunity to examine this potential relationship. In 1988, the first such investigation, conducted in Finland, suggested a higher incidence of schizophrenia among cohorts that were in utero during the second trimester of gestation, compared to unexposed birth cohorts (Mednick and colleagues 1988). Subsequent investigations of cohorts exposed to the 1957 epidemic in Great Britain (OCallaghan and colleagues), Ireland (Cannon and others), Japan (Kunugi and others) and Australia (McGrath and others) replicated the initial finding, and all but one showed second trimester specificity for the association.

Other studies have attempted to relate the occurrence of influenza epidemics over extended time periods to the births of preschizophrenics. Significant associations were demonstrated between exposure to second trimester prenatal influenza and schizophrenia for birth cohorts in Denmark (Barr and others), and England and Wales (Sham and others; Adams and others).

However, not all investigators have found this association. Crow and colleagues reported no increased risk of schizophrenia in a study using individual rather than group data on a cohort that was in utero during the second trimester of the 1957 influenza epidemic. Yet, this study has been criticized, since exposure data were derived from maternal reports of influenza following delivery, which are subject to underreporting. Other negative studies include those by Torrey and others in 10 states of the United States, Susser and others in Holland 1994, and Erlenmeyer-Kimling and others in Croatia.

Thus, the question of prenatal influenza exposure as a risk factor for schizophrenia remains unresolved. We believe that the inherent limitations of the research designs used in these studies lie at the root of the uncertainty. First, most of these studies utilized data that applied to groups rather than to individuals (i.e., it was known whether a woman was in the second trimester of pregnancy during a month in a peak period of an influenza epidemic, but not whether the woman had influenza). Second, there was no serological documentation of influenza exposure among individual pregnancies. It is unlikely that this controversy will be resolved until advancements are made to more sophisticated methods.

Relationships between prenatal exposure to several other infectious agents, including measles, polio and varicella-zoster virus, have also been demonstrated (Torrey and others 1988), although few studies have been conducted.

**Prenatal nutritional deprivation.**

One of the best documented exposures with adverse developmental central nervous system effects is prenatal nutritional deficiency (Brown and colleagues; Butler and others). In the search for specific nutritional factors in schizophrenia, our attention has focused on micronutrient deficiencies, in part because they occur in both the developed and developing world (Little and Elwood), as does schizophrenia (Jablensky and others). The most well-known class of neurodevelopmental disorders caused by a micronutrient deficiency consists of neural tube defects (NTDs), which include spina bifida and anencephaly; these CNS malformations result from a failure of neural tube closure.

Convincing evidence that folate supplementation in early gestation dramatically reduces the risk of NTDs (MRC Vitamin Research Study Group), suggesting that either a relative or absolute deficiency of prenatal folate is a cause of NTDs. As for micronutrient deficiencies, the prevalence of NTDs follows no simple gradient across rich and poor countries.
The Dutch Famine Study
A series of investigations by our group on the effects of the Dutch Hunger Winter of 1944 to 1945 has demonstrated an association between severe prenatal nutritional deprivation and schizophrenia (Susser and Lin; Susser and others [submitted]; Brown and others). Toward the end of World War II, the Nazi blockade of occupied western Holland led to a severe famine in that area. Since the famine was both sudden and time-limited, and relatively complete data on health outcomes in the population were available, it was possible to relate the degree and timing of nutritional deprivation to a variety of reproductive indices and CNS anomalies (such as NTDs) (Stein and others) and, a generation later, to the occurrence of schizophrenia. We found a significant greater than twofold effect of severe famine exposure in early gestation on the risk of hospitalized schizophrenia in both male and female offspring. Moreover, we observed a remarkable concordance between the occurrence of schizophrenia and congenital neural defects (including spina bifida and anencephaly) following severe famine in early gestation, suggesting that prenatal folate deficiency should be further investigated as a potential causal factor in schizophrenia.

Perinatal trauma.

Perinatal traumatic events, such as obstetric complications (OCs), can cause brain damage in the newborn and may also contribute to the etiology of neurodevelopmental disorders. In particular, perinatal trauma is proposed to contribute to the etiology of cerebral palsy (Nelson and Ellenberg) and mental retardation (Broman).

Associations between the number and/or severity of obstetric complications and the risk of schizophrenia in the offspring have been reported in many studies (McNeil and Kaj; Lewis and Murray); several indicators of prenatal or perinatal insults, including decreased head circumference, low birth weight or respiratory difficulty, appear to occur more frequently in infants who developed schizophrenia in adulthood compared to controls (McNeil and Kaj). These studies, however, relied upon retrospective data, which are subject to inaccurate reporting of events and recall bias. Indeed, the only study of OCs and schizophrenia in which obstetric histories were prospectively collected did not replicate the association between OCs and schizophrenia (Done and others).

It is clear that much research work remains as we attempt to further elucidate the role of prenatal risk factors in schizophrenia. Our group has embarked upon a series of exciting collaborative birth cohort studies aimed at uncovering these neurodevelopmental etiologies using novel approaches and strategies. These investigations are designed to address the limitations of prior studies, which include crude prenatal exposure data, inadequate control of bias due to loss to follow-up, and inadequate statistical power. As an illustration, we shall briefly describe the most advanced of these studies, the Prenatal Determinants of Schizophrenia (PDS) study.

The PDS study is based on the California Child Health and Development Study (CHDS), which included almost 20,000 live births from 1959 to 1966 in Oakland, Calif. The primary goal of the PDS is to examine relationships between specific prenatal exposures and the later development of schizophrenia in cohort members. A unique feature of this study is the availability of serum samples drawn during the pregnancies of the mothers of cohort members. The analysis of these serum samples will provide us with an opportunity to precisely quantify the nature and degree of a variety of putative prenatal exposures, and relate them to the occurrence of schizophrenia in the offspring. For example, Hollister and others (in press) have reported an association between Rh incompatibility and schizophrenia; we will attempt to replicate this finding in the PDS cohort.

We plan to utilize precise data on prenatal exposures from the PDS study in conjunction with family history and other genetic data from PDS families. Gene-environment studies that we plan to initiate include a suspected interaction between prenatal folate intake and a genetic abnormality of folate metabolism in the pathogenesis of schizophrenia.

For many years, researchers have proposed that schizophrenia might have neurodevelopmental etiologies, and hypothesized that several prenatal environmental factors could be potential causal agents. However, we have only recently witnessed the emergence of epidemiologic evidence implicating specific prenatal risk factors in schizophrenia. We are now on the threshold of the next phase of research in this field, in which sophisticated new designs will yield increasingly precise data on the gestational environmental exposures, opening new vistas for epidemiologic research on the
causes of schizophrenia.

References: References


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