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PRENATAL MALNUTRITION AND RISK OF SCHIZOPHRENIA

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Characterized by delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, schizophrenia is a severe mental disorder that is estimated to have a lifetime risk of one percent (Liu et al., Allen 2002). Prevalence rates in different countries range from 0.2-2.0 percent with an average incidence rate of 28.1 per 100,000 remaining stable across a wide range of cultures, climates and ethnic groups (Thomas 2000). In the United States, at any given time there may be two to three million people who either have schizophrenia or are at risk of developing it (Allen 2002). The disease usually manifests itself in late adolescence or early adulthood, and has nearly equal rates of prevalence among women and men. Schizophrenia is a brain disease, not simply a psychological disorder. At autopsy, the schizophrenic brain weighs about five percent less than a normal brain, and the ventricles are noticeably enlarged. In fact, every brain region is affected by schizophrenia (ibid).

While there are many suspected causal factors to schizophrenia, researchers still do not understand the factors necessary to produce schizophrenia and there is no known single cause that produces schizophrenia (Allen 2002). There is sufficient evidence to support a genetic link. Researchers have conducted a variety of pedigree, twin and adoption studies, all of which indicate the risk of developing schizophrenia is increased 10-fold if there is a first degree relative with the disease (ibid). Other associations concerning this disease have been made. Research suggests that a biological injury experienced early in the gestation period can lead to increased risk of schizophrenia. This biological injury may include fetal exposure to infectious diseases, psychological distress experienced by mothers or severe malnutrition (Davis and Bracha 1996:401). This paper will discuss the latter cause, malnutrition, which has recently been identified as a possible causal factor to schizophrenia, and explore the epidemiological investigations, which reveal an association between malnutrition and schizophrenia.

Malnutrition refers to a state in which an individual does not have access to sufficient quantities of food or is not able to receive all the nutrients from the food available. Malnutrition can occur in situations of excess in which one is over nourished but not receiving proper nutrition, but for the purposes of this inquiry, malnutrition refers to a lack of nutrient resources. There are several different forms of malnutrition. Mild-to-moderate malnutrition (MMM) is the most common form. Individuals experiencing MMM may be receiving enough food, but their food intake is lacking in nutrients needed for healthy living. It is most likely, however, that severe malnutrition, or protein-energy malnutrition is responsible for schizophrenia. Severe malnutrition occurs when an individual does not receive enough food and therefore is deficient in protein to energy intake and is also lacking a great majority of the nutrients necessary for survival.

Individuals without adequate nourishment are at an increased risk for many diseases and conditions. Those who are malnourished are a greater risk of contracting infectious diseases due to diminished resistance, and are less able to recover due to a compromised

immunity. Although, a malnourished individual may not suffer any more bouts of illness or disease than a properly nourished person, but these bouts will be longer in duration because of a decreased ability to recover (Schroeder 2002:405). It is well-known that fetuses are affected by maternal nutrition, and malnutrition experienced in the gestation stage can lead to many health complications including low birth weight, compromised immunity and impaired physical and neurological development. Further, studies have provided evidence that severe malnutrition in the early months of development can lead to schizophrenia in later life. The implication of this is that there may be some forms of schizophrenia that are, in fact, preventable (Bower 1996:68). The remainder of this paper will include a discussion of research that has been conducted thus far concerning the association between schizophrenia and malnutrition.

Few studies have been done regarding the association between prenatal malnutrition and schizophrenia. There are two main reasons for this lack of exploration. First, schizophrenia is a highly complex condition and there are many causal factors that are associated with an increased risk. A strong genetic link has been identified through the use of twin, pedigree and adoption studies. In addition, several environmental factors have been associated with an increased risk of schizophrenia, including postnatal undernutrition (Cordero et al.) and place and season of birth (Mortensen et al. 1999). Furthermore, malnutrition is one of many prenatal conditions that can lead to schizophrenia. Verdoux et al. (1997) tested the hypothesis that obstetric complications taken as a whole lead to more frequent cases of schizophrenia. Using subjects identified from previous published and unpublished studies, they found that a history of obstetric complications is twice a frequent among schizophrenic than among control, and further the earlier the age of onset, the more likely a history of obstetric complications. In this study, malnutrition was not differentiated from other obstetric complications.

The other, and perhaps more important, reason for the lack of studies is the ethical concern. It is not humanely possible to test the effects of prenatal malnutrition using human subjects. Therefore, the studies that have been conducted are either laboratory tests using rats as test subjects or retrospective cohort studies using subjects conceived or born during a known period of high famine in a given region.

Randomized Trials

Evidence for an association between prenatal undernutrition and schizophrenia has been tested in various manners using rat subjects. The benefit of such tests is that specific genes and nutrients can be isolated in order to determine the specific causal factors. A drawback, however, is that rat brains are not as developed at birth as are human brains. The human brain develops greatly during gestation unlike animals. In addition, most studies conducted using rats are primarily concerned with neurodevelopment as a whole and do not focus specifically on schizophrenia. Therefore, while the studies are instrumental in determining connections and future areas of research, no conclusive statements regarding the human physiology can be made.

Results of randomized trials determined that nutrition is probably the single greatest environmental influence on the fetus and is central to functional and neurological development (Dauncey and Bicknell 1999). In specific, protein malnutrition was found

to adversely affect the brain in many ways. In one such study, two groups of rat dams were fed diets with differing levels of protein during gestation, birth and weaning in order to test the long-term effects of prenatal protein deprivation. They found that even when protein rehabilitation was begun at birth, the neurological effects of prenatal deficiencies were not reversed or significantly ameliorated. They concluded, therefore, "prenatal protein deficiency results in long-lasting changes in neuronal systems in the hippocampal formation" (Dauncey and Bicknell 199).

Other preclinical studies have been conducted regarding the association between prenatal nutrition and neurological development. Jordan et al. (1981) found that prenatal undernutrition impaired spatial learning. In separate studies Lewis et al. (1979) and Bedi (1991) found that prenatal and early postnatal malnutrition had a noticeable affect on brain cell counts. Finally, Kawamato and Halas (1984) and Golub et al. (1983) look specifically at the role of zinc in brain development. Although these studies help to understand the role of nutrition in brain development, none address the specific association between undernutrition and schizophrenia.

At least one experiment tested the possibility the impact of prenatal nutrition on schizophrenia in later life. Palmer et al. tested the effects of prenatal protein deprivation on prepulse inhibition (PPI) of the startle response, which is directly relevant to the development of schizophrenia. They hypothesized that prenatal protein deficient rats would exhibit deficits in PPI and these deficits would be accompanied by changes in the central neurotransmitter systems associated with schizophrenia. For the test, dams were fed with a normal or a low protein diet five weeks prior to insemination and throughout gestation. At birth, all dams were switched to a normal protein diet. Initially, there were no differences between the two groups, but at a second time point, which more closely resembles young adulthood, the protein deficient rats had significantly lower PPI than the control group. Furthermore, the study found that prenatal protein deficient rats exhibited significantly reduced startle reactivity. Therefore, their findings supported their hypothesis that prenatal malnutrition can trigger behavioral abnormalities associated with schizophrenia, and further, "the onset of PPI deficits as animals mature into adulthood supports the congruence of the model with human psychopathology" (Palmer et al. 2004).

Dutch Hunger Winter

Few studies in humans have been conducted regarding the association between malnutrition and schizophrenia, and of those that have been done most have relied on data from the Dutch famine study, a study which represents an almost perfect natural experiment. During World War II, the Netherlands experienced a great famine that began in October 1944, reached its peak in February and April 1945, and ended with liberation in May 1945. During the height of the famine, malnutrition was the leading cause of death - more than 20,000 people died of famine-related causes (Susser, Hoek, Brown 1998). According to Brown et al. (2000), "The tragic circumstances of the Dutch Hunger Winter created a unique opportunity to examine the relation between exposure to prenatal famine and psychiatric illnesses requiring hospitalization, including major affective disorder."

The Dutch Hunger Winter occurred at a precisely circumscribed time and place and in a society able to document the impacts of the famine (Susser et al. 1998). The data collected have been used to study the effects of prenatal malnutrition on neurological development and has proved to be a strong data set in that 1) it is difficult to misclassify on the basis of birth as the time lines are clearly delineated and 2) the potential for confounders is minimized because the exposed (conceived during the famine) and unexposed groups (conceived before or after the famine) share great similarities (Susser et al. 1998).

Susser et al. (1996) used information to conduct a retrospective cohort study testing the hypothesis that early prenatal nutritional deficiency is associated with an increased risk for schizophrenia. They compared birth cohorts from six Dutch cities most affected by the famine exposed to nutritional deficiencies with those unexposed in regards to hospitalizations for schizophrenia in adulthood. Three criteria were used to assess exposure: 1) low food rations during the first trimester, 2) conception during the height of the famine (February to April 1945), 3) increased congenital neural defects. They defined three birth cohorts: those conceived at the height of the famines, those conceived during the famine but before the height, and those unexposed, not conceived during the famine. Cases of schizophrenia were determined using the Dutch psychiatry registry and their findings revealed a two-fold increase in the risk of schizophrenia for those conceived at the height of the Dutch Hunger Winter. In addition, although an earlier, more limited study showed increased rates of schizophrenia in women, the gendered implications did not hold in this study.

Drawing upon the results of this study, a further investigation (Hoek et al. 1996) tested the association between prenatal malnutrition and schizophrenia, but did not limit study population to those who had been admitted to the hospital. Instead, they derived information regarding cases of schizoid personality disorder from military induction. This study more closely resembles a case control study in that those with schizoid personality were identified as cases, and those diagnosed with psychoneurosis, the most common diagnosis among military inductees, were the controls. However, the focus in this study is still on exposure and the same exposure groups were used. Their findings reproduced what was found in the previous study. Those conceived during the height of the famine had a significantly greater risk of schizophrenia but no greater risk of psychoneurosis than those conceived at other times during the famine or not during the famine.

This apparent association between prenatal malnutrition and schizophrenia may be due to other factors. For example, in times of famine, individuals may ingest certain materials not commonly eaten, and it is the ingestion of these items that increases the risk of schizophrenia. There is, however, no strong evidence to support this claim. In addition, these studies merely identify an association. Based on their findings, it is not possible to determine if a specific micronutrient deficiency is implicated or if nutritional deficiency works in conjunction with other genetic factors to increase schizophrenia risk.

There have been few studies that have attempted to discover the specific causal agents in the relationship between prenatal malnutrition and schizophrenia. Hulshoff et al. (2000) looked at the association between prenatal nutritional deficiencies and brain abnormalities associated with schizophrenia. They conducted a cohort study in which the

nine schizophrenics and nine healthy individuals who had been conceived during the height of the famine were compared with nine healthy and nine schizophrenic individuals who were not exposed to prenatal famine. Brain abnormalities were found in six of the subjects exposed to prenatal famine and in one individual not exposed. The researchers concluded that, "exposure during the first trimester of fetal development to the Dutch Hunger Winter of 1945 was associated with an increase in the incidence of brain abnormalities, in particular of focal white matter hyperintensities." This study provides further evidence for the relationship between malnutrition and schizophrenia, and also implies that this relationship exists at a structural/functional level. The study is limited due to a small sample size, but is supported by other similar studies.

Brown et al. (1996) attempt to ascertain the specific nutrient deficiency implicated in schizophrenia. They review more than 30 studies that test the relationship between nutrition and neurological development. They review several studies that test the affect of folate, zinc and B12, and although none of these studies are directly concerned with schizophrenia, they do demonstrate that prenatal nutrient deprivation results in neuropathy similar in nature and location to schizophrenia. The investigator rightly claimed the need for further testing in this arena and made suggestions for two further studies. The first is a cohort study. In California, approximately 12,000 women underwent extensive prenatal and perinatal testing between 1959 and 1966. The researchers plan to identify cases of schizophrenia among the offspring of these women and conduct seriological analyses to determine nutritional factors during pregnancy. The second type of study recommended is more animal studies looking at the relationship between nutritional deficiencies and specific neuropathies associated with schizophrenia.

Other Studies

Among studies conducted with human subjects concerned with the association of prenatal malnutrition with schizophrenia, only one study that I found did not use data from the Dutch Hunger Winter. Liu et al. (2003) conducted a case-control study testing the frequency of alleles _2,3,4 of apolipoprotein E (apoE) gene among Chinese patients. Cases were patients with schizophrenia born between 1920 and 1978 and were identified via Shanghai Mental Health Centre. Controls were selected from Shanghai general outpatient clinics and were screened for the absence of mental illness. The researchers took blood samples and screened for frequencies of the apoE gene. Their findings revealed an association between the APOE genotype and frequency, but their data revealed something more. They discovered that while all patients with schizophrenia show some degree of apoE association, the only significant contributions come from those patients born during two periods of food deprivation in China. The researchers comment,

> *"Had our schizophrenic cohort not included cases born during these exceptional times, our study would have resembled most of the others reported to date and been essentially negative. Instead, we may have inadvertently uncovered a potentially important gene/environment interaction."*

They conclude that the apoE gene may operate as an additional risk factor for schizophrenia in individuals subject to prenatal or early postnatal malnutrition. This study represents the direction Brown et al. (1996) argue research of malnutrition and schizophrenia association needs to turn. That is, the association has been shown, and now it is essential to determine the specifics of this association.

Limitations

All of these studies are limited because randomized trials or large-scale studies cannot be conducted due to ethical considerations. Therefore, researchers are limited to analyzing available data and subjects. Additionally, because of the limited study population there may be certain confounders that have not been fully explored. Davis and Bracha (1996) argue that it is perhaps the re-feeding after the famine that leads to an increased risk of schizophrenia. They postulate that thiamine stores become depleted during malnourishment, but re-feeding precipitates an even more severe thiamine deficiency. Therefore, they argue that beriberi caused by a thiamine deficiency brought on by excess food after famine, could be the cause of increased risk of schizophrenia.

Van Os (1997) argues that social class may also play a role in the association between prenatal malnutrition and schizophrenia. Those in a higher social class may be more likely to be affected by famine as those in lower social classes often are faced with depleted food sources. Therefore, famine in lower classes does not create the same physiological response as it would among those for whom food supply is not an issue. However, in the case of the Dutch Hunger Winter, social class had ceased to be much of a factor, as most of the food and supplies had been rationed for many years prior to the famine.

Finally, these studies are limited because more work needs to be done regarding underlying factors in the association between malnutrition and schizophrenia. If, as is argued in this paper, prenatal malnutrition is a causal factor of schizophrenia, some cases of schizophrenia may be preventable if malnutrition can be curbed. However, it first may be necessary to determine which nutrient or possibly genetic markers are implicated. For example, if an increased risk of schizophrenia is due to a thiamine deficiency as Davis and Bracha (1996) argue, simply "refeeding" a famished population will only exacerbate the problem. Therefore, this is an area which demands further research.

Further Research and Conclusions

The relationship between prenatal malnutrition and schizophrenia helps to further clarify the impact that poor nutrition has on an individual throughout the lifespan. Although the studies discussed above are concerned primarily with isolated cases and easily demarcated times of hunger or famine, they can be used to formulate hypothesis about malnutrition and schizophrenia among those who live in constant hunger. Specifically, people living in poverty are at a constant risk of hunger and famine. No studies were found that examined this relationship, and statistics do not support the claim that in regions of high consistent famine the risk of schizophrenia is greater. Indeed, there is a constant prevalence rate across regions. However, there are several possible explanations for this rate.

First, although the prevalence rate is constant, the incidence rate is higher in some regions (Thomas 2000). Research may reveal that there are higher incidence rates in high poverty, high malnutrition regions in which people are also less likely to survive. Second, chronic malnutrition is often associated with high rates of other health problems such as infectious diseases and poor access to health care. These health problems could limit a person's chances of living long enough to be diagnosed with schizophrenia and lessen women's fertility so that there are fewer births (Brown et al. 1996). Third, areas of high malnutrition also most often are areas with poor health care systems such that a diagnosis of schizophrenia is not likely to be made. In addition, in non-U.S. settings, cultural understandings may differ and a mental disorder identifiable as schizophrenia will be known as something else in that culture.

Finally, people living in chronic malnutrition often develop coping mechanisms that those going through a short-term famine do not develop. For example, Rigoberta Menchú describes her experiences living in Guatemala during a period known as La Violencia. During this extended time, the Mayan Indians lived in great poverty and hunger. She explains that pregnant women would take many relaxing baths during the day for "how else would a woman who endured hunger and hard work, give birth to healthy babies?" (Burgos-Debray 1984).

It could be argued that the association between malnutrition and schizophrenia does not need to be studied. After all, malnutrition leads to many complications such as decreased immunity to infectious diseases, impaired physical and mental development and early death. Schizophrenia has many causes including genetic factors, environmental conditions and all obstetric complications. We need to know as much as possible about the impacts of malnutrition in total. In addition, if indeed we can prevent schizophrenia by ensuring proper nutrition, this is an arena of research that most definitely needs to be explored. Finally, as schizophrenia is an extremely complex disorder, the more that is known about it, the more equipped we are to work towards a cure and/or prevention. Therefore, it is essential that researchers and investigators continue to explore the links between prenatal malnutrition and schizophrenia.

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