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Schizophrenia and Neural Tube Defects: Comparisons From an Epidemiological Perspective

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In this review, we examine and compare epidemiological studies of schizophrenia and neural tube defects (NTDs). Although there is no apparent link between these 2 disparate disorders in terms of clinical manifestation or phenotypes, overlapping patterns in the variation of incidence of schizophrenia with that of NTDs indicate the existence of one or more shared etiological risk factors. Evidence in support of such a phenomenon may enhance our understanding of underlying pathological mechanisms and may guide future studies of etiology and prevention. The similarities that occur in a number of epidemiological observations for these disorders are in keeping with a hypothesis of nutritional deficiencies in utero acting as a risk factor for both schizophrenia and NTDs. Programes of periconceptual folate and multivitamin supplementation aimed to reduce the risk of NTDs are already in place in many countries. Nevertheless, evidence of additional effects of specific maternal micronutrient deficiency on risk of schizophrenia may not only increase enthusiasm for expansion of such programes but also enhance understanding of etiology of this disorder and offer the potential for targeted interventions in high-risk groups.

Key words: epidemiology/folic acid/5,10-methylenetetrahydrofolate reductase/micronutrients/neural tube defects/schizophrenia

Introduction

A number of similarities can be observed in epidemiological studies of schizophrenia and neural tube defects (NTDs). Evidence of overlapping patterns in the variation of incidence of these 2 disorders may indicate one or more shared etiological risk factors and may enhance our understanding of underlying pathological mechanisms.

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Schizophrenia is a mental disorder characterized by delusions, hallucinations, disorganized thought and speech, and negative symptoms that encompass deficits in expressing emotions and initiating goal-directed activity. Incidence of schizophrenia is approximately 0.07–0.43 per 1000 per year, with onset usually between the ages of 15–55.[1] Although there are no clearly defined pathological abnormalities that characterize this disorder, schizophrenia is associated with a number of neuroanatomical, neurochemical, and functional neuroimaging disturbances that provide strong evidence for a largely biological basis for this disorder.[2,3]

NTDs are congenital abnormalities involving a failure of the neural tube to close during the fourth week of embryogenesis. Defects can occur anywhere along the formation of the spinal cord. They include anencephaly that occurs at the cranial end of the neural tube, and spina bifida, a usually less severe defect involving spinal structures. Incidence of NTDs is approximately 0.5–10 per 1000 births.[4–6]

Understanding of the etiology of NTDs is far from clear, but nevertheless it is substantially easier to study the epidemiology and etiology of this group of disorders than it is for schizophrenia for a number of reasons. NTDs are diagnosed relatively easily, though etiological heterogeneity, eg, at level of the lesion, undoubtedly exists.[7] Animal models are readily available to study etiological mechanisms while intervention studies in humans are relatively feasible given the short time window from period of possible exposure to development of the defect.

In schizophrenia, however, the situation is more complex. First, diagnosis relies mainly on subjective descriptions of unusual, and often difficult to describe, experiences. Less reliance is placed on objective measures, and those that are utilized such as observations of thought disorder and negative symptoms are difficult to measure reliably. Second, there is often wide variation in clinical presentations such that there may be no overlap in symptoms between 2 individuals diagnosed with schizophrenia, leading to uncertainty about both the validity as well as reliability of schizophrenia as a diagnosis. Third, as schizophrenia develops in adult life it is more difficult to measure incidence accurately than it is for

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Table 1. Summary of Overlapping Patterns of Risk for NTDs and Schizophrenia

	NTDs	Schizophrenia
Famine studies	↑ risk in offspring of women pregnant during Dutch and German famines	↑ risk in offspring of women pregnant during Dutch and Chinese famines
Temporal trend	↓ incidence over past few decades	Some evidence of ↓ incidence over past few decades
Season of birth effects	Some evidence of ↑ risk in spring-summer conceptions (winter-spring births)	↑ risk in winter-spring births
Maternal febrile/flu-like illness	↑ risk	↑ risk
Raised maternal BMI	Some evidence of ↑ risk	Some evidence of ↑ risk
Maternal diabetes	Some evidence of ↑ risk	Some evidence of ↑ risk
Short birth spacing interval	Some evidence of ↑ risk	Some evidence of ↑ risk
Parity	Some evidence that multiparity and primiparity both ↑ risk	Some evidence that multiparity and primiparity both ↑ risk
MTHFR C677T genotype	↑ risk in both maternal and fetal TT homozygotes	↑ risk in TT homozygotes
Homocysteine	↑ risk in maternal hyperhomocysteinemia	↑ risk in subjects with hyperhomocysteinemia

Note: NTDs, neural tube defects; BMI, body mass index; MTHFR, methylenetetrahydrofolate reductase.

NTDs, with most studies using the time of presentation to clinical services as an index of true incidence. Furthermore, the long window of potential exposure to etiological factors over the life course (periconceptually through to adulthood) increases the complexity of both observational studies and potential interventional experiments.

Problems in determining true incidence exist for NTDs too with regard to the identification of defects in stillbirths and abortions, especially, over the past 3 decades with the increase in elective terminations following antenatal screening. Nevertheless, the epidemiology and etiology for NTDs is easier to study and better understood than for schizophrenia, in part due to the reasons outlined briefly above.

Although there is no apparent link between NTDs and schizophrenia in terms of clinical manifestation or phenotypes, epidemiological evidence lends some support for a shared etiological process between these 2 disorders. In this review, we examine and compare epidemiological studies of these 2 disparate disorders. The main areas in overlapping patterns of risk are summarized in table 1. Etiologically relevant exposures for schizophrenia that operate past the period of risk for NTDs, taken here as being past the first trimester of pregnancy, are not discussed as there can be no comparison for NTDs.

Epidemiological Findings Consistent with a Shared Aetiological Risk Factor

The most important advance in the understanding of NTDs over recent years has been evidence from randomized controlled trials (RCTs) demonstrating a reduction in incidence and recurrence of NTDs following introduction of periconceptual folate supplementation.[8,9] The role of folate and possibly other micronutrient deficiency is supported by observational epidemiological findings and animal model studies.[10] Associations of NTDs with lower socio-economic groups,[11] a decreasing trend in incidence over the past century,[12] the presence of postfamine peaks,[13] and seasonal variation in incidence[14] are all consistent with, and probably secondary to, the contribution of diet to their etiology. Patterns of variation in incidence of NTDs that may be attributable in part to folate deficiency show considerable overlap, as we discuss below, with variation in incidence of schizophrenia.

Famine Studies

Peaks in incidence of NTDs had been reported following both the Dutch and German famines during World War II, with the greatest risk in the cohort of women exposed to the famine during their first trimester of pregnancy.[13,15] Although these were ecological studies and therefore particularly susceptible to confounding, they indicated nevertheless that nutritional deficits periconceptually or in early gestation may be important in the etiology of NTDs, as confirmed subsequently by RCTs of folate supplementation.[8,9] The same Dutch birth cohort has also been shown to have an increased rate of schizophrenia compared with birth-year cohorts not exposed to famine in utero,[16] with recent support from findings from a Chinese cohort exposed to famine.[17] The most likely explanation for the sharp rise in incidence of schizophrenia in these cohorts is that nutrient deficiency, possibly of folate or other micronutrients during early gestation increases risk of schizophrenia as well as NTDs.

If sharp increases in incidence of NTDs and schizophrenia following periods of famine are due to nutrient deficiency, other similarities in the pattern of incidence of these disorders might be expected, including reduction in incidence as nutritional status of pregnant women increases, increased risk at times of higher risk of nutrient depletion, and geographical variation reflecting spatial patterns of nutrient availability.

Temporal Trends in Incidence

Over the past 30 years, the incidence of NTDs has decreased substantially, and this appears to be independent of the increase in elective terminations following antenatal diagnosis that has occurred over the past few decades.[6,12] This is likely to be due, at least in part, to the improved nutritional status of women periconceptually. A trend for decreasing incidence of schizophrenia over the past few decades had also been reported by a number of studies, with both period and birth-cohort effects probably contributing to this decrease over time.[18,19] Although this could, in part, be due to changes in admission policies for first-onset episodes of schizophrenia and changing diagnostic practices, it is unlikely that this would explain all the reduction in incidence observed.[20] The evidence for a decrease in schizophrenia incidence is not as clear as that for NTDs, perhaps as a result of a concurrent rise in other putative risk factors, such as increasing paternal age or cannabis use,[21,22] which would obscure or counteract a temporal trend of diminishing incidence of this disorder driven by improved nutritional status of women periconceptually.

Season of Birth Effects

Peaks in incidence of NTDs have been reported from a number of studies for spring-summer conceptions (resulting in winter-spring births) particularly for anencephalus.[14,23] Seasonal variation is also one of the most interesting and clearly replicated findings for schizophrenia, with an approximately 5%–8% increase in risk for subjects born in the late winter and early spring months in both the northern and southern hemispheres.[24] Seasonal variation of micronutrient levels, including folate, has been observed in foods and in maternal serum[25–27] and may account for the patterns of seasonal variation in incidence of these disorders. Interestingly, the relationship between seasonal variation and NTDs has diminished over time,[14] and one possible explanation for this may be the increased availability of nutrient-rich produce all year round over recent decades. Although this pattern of risk is consistent with a theory of variation in nutrient availability, other plausible explanations such as seasonal variation in exposure to infections, environmental toxins, or sunlight have also been proposed as alternative explanations for both disorders.

Associations With Maternal-Related Factors

Nutrient depletion is more likely to occur in the presence of short birth spacing intervals as it may take many months to replenish most micronutrient stores, and up to a year to replenish folate levels, after pregnancy.[28] Short birth interval is associated with increased risk of NTDs[29,30] and other (non-NTD) congenital malformations and a similar association has been reported in schizophrenia.[31,32] Other maternal-related factors, some of which may be influenced by nutritional status show similar, though perhaps less robust patterns across these 2 disorders. For example, a maternal ''flu-like'' or febrile illness in the first trimester has been associated with increased risk of NTDs.[33,34] A similar association with maternal exposure to infection during pregnancy is seen in schizophrenia, though it seems to be second rather than first trimester exposure that is more strongly associated with risk.[35,36] Associations with maternal hyperthermia and infection during pregnancy could be mediated through direct effects of an infective or immune reactive process on embryonic development,[37,38] although it is also possible that these associations may be secondary to, or confounded by, a nutrient-deficient state. Incidence of both NTDs and schizophrenia also appear to be increased by multiple gestation,[6,39] having 3 or more previous pregnancies,[6,40] primiparity,[6,40,41] increased maternal body mass index,[42,43] and by the presence of maternal diabetes.[5,44] However, although overlapping patterns in risk exist for a number of maternal-related factors across the 2 disorders, it is not clear to what extent, if any, these associations are explained by shared etiological factors.

Geographical Variation

Patterns in geographical variation of incidence of a disorder may provide clues about etiology. In many developing countries, where nutritional status is likely to be poorer than developed countries, a consistent pattern of higher incidence of NTDs is not observed, despite the role of folate in the etiology of this disorder. However, estimates of wealth or development of a country are unlikely to be a good reflection of folate status of the population. Ecological correlation between lower mean serum folate levels in women and elevated rates of NTDs is seen, eg, in Northern compared with Southern regions of China[4,45] and is consistent with our understanding of folate on risk of NTDs. However, NTDs are of multifactorial complex etiology, and therefore, variation in other factors may partially or completely obscure any pattern related to distribution of folate availability.

A number of areas show overlapping patterns of increased or reduced rates of both NTDs and schizophrenia. For example, higher than average rates of both NTDs and schizophrenia have been reported from the

Republic of Ireland, the Punjab and Tamil Nadu regions of India, and in Eastern as compared with Western Canada.[1,4] One would expect some overlap in pattern of incidence between these disorders even if there was no shared etiological component, however, and it is unclear whether the patterns observed from detailed reviews of geographical variation in incidence of these disorders are more than one would expect by chance alone.[1,4] Differences in ascertainment and diagnostic practices between studies, as well as the presence of etiological heterogeneity, make attempts to observe overlapping patterns of geographical distribution across these 2 disorders particularly difficult to interpret.

A consistent pattern of increased risk of schizophrenia is seen in subjects born in urban as opposed to rural areas, with some evidence of a dose-response effect related to the number of years spent living in urban regions.[46] Higher rates of NTDs have been reported in urban areas in both the British Isles and North America,[4] though evidence for this association is much less consistent than that observed in schizophrenia.[4,47]

Genetic and Molecular Studies

As a consequence of the demonstrated protective effects of folate supplementation on risk of NTDs, there has been substantial interest in the role of genes involved in folate-related metabolic pathways on risk of NTDs. Although a large number of candidate genes have been examined in relation to risk of NTDs from both human and animal model studies, the most consistent evidence has been for an association with the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene.[10,48,49] MTHFR enzymatic activity on the dietary folate metabolite 5,10-MTHF is responsible for conversion of homocysteine to methionine, which is required for DNA methylation. Variation at the C677T site in this gene results in a thermolabile protein with reduced enzymatic activity that has been linked to variation in both serum homocysteine and folate levels.[50,51] A meta-analysis of this polymorphism found associations between both maternal and fetal TT (reduced activity) genotype and risk of NTDs.[49] Evidence from meta-analyses also support a similar association of this same variant with schizophrenia.[52,53] Furthermore, consistent with a hypothesis of aberrant folate pathway function as an etiological agent for these disorders, case-control studies of subjects with schizophrenia and of mothers of children born with NTDs both report elevated plasma levels of homocysteine.[53,54]

Conclusion

It is not the aim of this review to encompass all epidemiological findings for both NTDs and schizophrenia within one etiological framework. Nevertheless, findings from epidemiological studies of famine effects during pregnancy and overlapping patterns of risk distribution suggest that maternal micronutrient deficiency may play an important causal role in both disorders. Furthermore, evidence from genetic studies of MTHFR implicates folate as a potentially important micronutrient in the etiology of schizophrenia as well as of NTDs. Although not presented in detail here, there are also a number of epidemiological areas where findings for NTDs and schizophrenia fail to concur or indeed show opposite effects. This would not be unexpected for any 2 disorders of multifactorial etiology, even if some risk factors were shared between the 2 disorders.

If micronutrient deficiency does indeed increase risk of both NTDs and schizophrenia, comorbidity of these 2 disorders might be expected. There is no overlap in the signs or symptoms of schizophrenia and NTDs. However, minor physical anomalies, mainly of craniofacial morphology, occur more commonly in schizophrenia[55] and suggest some subtle problems in embryonic development even if the pathways involved may not be specifically related to those for NTDs.

There are no studies to date as far as we are aware that have examined associations between comorbidity of the 2 disorders. In fact, given the low incidence of both schizophrenia (approximately 15 per 10 000 people per year) and NTDs (approximately 7 per 10 000 live births per year), sample sizes required to demonstrate even a strong association between these disorders would be larger than are available for most studies to date. Assuming an incidence rate for NTDs as above, it would need a sample of over 4000 individuals with schizophrenia and 3 times the number of controls to have 80% power to demonstrate a 4-fold increase in prevalence of NTDs and over 20 000 cases to demonstrate a 2-fold increase. The Scandinavian linkage data sets might able to detect a 4-fold increase in NTD prevalence in subjects with schizophrenia, but such a strong association between 2 multifactorial disorders seems inherently unlikely. Such data sets might be able to explore whether other established risk factors for NTDs such as maternal use of antiepileptic drugs during pregnancy[56] are associated with risk of schizophrenia, though again etiological heterogeneity means only weak associations might be observed even where shared etiological mechanisms exist.

Overall similarities in a number of epidemiological observations for these disorders are in keeping with a hypothesis of nutritional deficiencies in utero acting as a risk factor for both schizophrenia and NTDs. Future studies could focus on the effects of nutrient deficiencies in animal models on endophenotypes of schizophrenia such as deficits in attention, prepulse inhibition, and other sensory gating deficits, as well as cognitive, neuroanatomical, and neurochemical abnormalities that characterize this disorder. Nutrient supplementation of animal models with heritable abnormalities of such endophenotypes in utero through to adult development

may inform us about potential effects of nutrient supplements in modifying risk for schizophrenia.

Follow-up studies of RCTs of folate supplementation during pregnancy could examine whether risk of schizophrenia in the offspring is indeed reduced, as would be predicted if folate deficiency plays a role in the etiology of this disorder. Furthermore, follow-up of naturalistic cohorts where use of folate supplementation during pregnancy or, more informatively, where folate and other micronutrient levels periconceptually are recorded would help to establish the importance of nutrient deficiency during embryonic development on risk of schizophrenia. This might be particularly informative where genetic data on micronutrient metabolic pathway genes in both the mother and affected offspring was also available, especially, given preliminary evidence of potential interactions between genotype and markers of nutritional status in NTDs.[49] Animal models of NTDs resulting from a variety of environmental teratogens[57] and candidate genes knockouts[48] may also inform about potential exposures for further study of etiological mechanisms in schizophrenia, even though etiological heterogeneity makes it unlikely that the effects of most of these exposures would be shared across the 2 disorders.

Programes of periconceptual folate and multivitamin supplementation aimed to reduce the risk of NTDs are of course already in place in many countries, so evidence of additional effects of any micronutrient deficiency on risk of schizophrenia might not be expected to add much to public health policies, although it would increase enthusiasm for the expansion of such programes. Nevertheless, a clearer understanding of the role, if any, of micronutrients on the development of schizophrenia would enhance our knowledge of etiology of this disorder and, though such policies are not without problems, offer the potential for targeted interventions in high-risk groups.

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