Does global hypomethylation contribute to susceptibility to neural tube defects?1–3

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Neural tube defects (NTDs) are common, costly, and often times lethal human congenital malformations whose etiologies remain poorly understood. Without accounting for the small percentage of NTDs associated with chromosomal or single gene disorders, NTDs are believed to have a multifactorial etiology with a combination of both environmental and genetic factors contributing to their development. Specific risk factors for NTDs that have been identified include maternal diabetes mellitus (1), maternal obesity (2), maternal use of antiepileptic drugs such as valproic acid (3), maternal hyperthermia, and paternal occupation (4).

The preventive effect of folic acid on NTD risk has been subjected to extensive epidemiologic research (5), and the resulting evidence is compelling. The evidence includes the following: 1) consistent results from multiple study designs conducted in geographically disperse populations; 2) a reduction in NTD prevalence in the United States and other countries participating in mandatory food fortification programs; 3) lower red blood cell and serum folate concentrations among women who had previously given birth to an infant with an NTD; 4) elevated NTD risks associated with exposures to folate antagonist medications, primarily anticonvulsant drugs; and 5) the presence of high titers of blocking antibodies to the folate receptor x (6).

The effect of one-carbon metabolism on normal neural tube closure extends far beyond just folic acid. Lowered serum concentrations of vitamin B-12, independent of folate, have been associated with increased risks of NTDs (7). Furthermore, Shaw et al (8) used prospectively collected midgestational serum samples to examine potential associations between several serum nutrients related to one-carbon metabolism and NTD risk. They found no significant differences between serum folate and homocysteine concentrations in pregnancies complicated by an NTD compared with serum concentrations in control pregnancies. This absence of an association with serum folate could potentially be explained by the fact that the women in this study were from a population whose food supply was fortified with folic acid, and most of the mothers were taking prenatal vitamin supplements containing folic acid, unlike the population in the Shanxi Province Study. What was most striking in this study was the strong linear association between maternal total choline concentrations and decreased NTD risk. Like folate, choline is involved in one-carbon metabolism, contributing to cell membrane phospholipids. Phosphatidylcholine is required for cell membrane assembly, which is an ongoing critical event during embryogenesis. Nearly all of the choline taken up by the embryo is converted to phosphatidylcholine. During the period of neural tube closure, embryos cannot produce phosphatidylcholine and rely entirely on maternal uptake of choline to meet their developmental needs.

Epigenetic mechanisms play important roles in etiologies of complex diseases (4, 5). These mechanisms are thought to be involved in the complex etiology of NTDs. During early embryogenesis, DNA methylation, which is the chief regulator of gene expression, is epigenetically reprogrammed. Furthermore, it has been well established that methylation of DNA can be influenced by dietary contributions of methyl donors such as choline, folate, and methionine. Any suboptimal methyl-donor supply could alter DNA methylation and provide a ready explanation for a possible mechanism contributing to increased birth defect risk (9).

Disruption of embryonic methylation has been experimentally shown to be linked to NTDs (10). The observation that inactivation of the DNA methyltransferase DNMT3B disrupts de novo DNA methylation and causes multiple birth defects including NTDs in mice and underlines the importance of DNA methylation in relation to NTDs. Inhibition of the one-carbon metabolic enzymes methionine S-adenosyltransferase (MAT) and S-adenosylhomocysteine hydrolase in a chick embryo model resulted in widening of the anterior neuropore suggestive of abnormal neural tube closure along with a decreased S-adenosylmethionine/S-adenosylhomocysteine (AdoMet/AdoHcy) ratio, indicative of impaired methylation. Inhibition of MAT in cultured mouse embryos also decreased the AdoMet/AdoHcy ratio and induced NTDs (10). One human case report was published

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2 Supported by NIH grants NS05249 (GMS, RHF) and by the Margaret M Alkek Foundation.

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First published online April 7, 2010; doi: 10.3945/ajcn.2010.29534.
in which the mother of an NTD infant also had a decreased AdoMet/AdoHcy ratio (11).

A long-awaited study of the role epigenetic factors play in determining susceptibility to human NTDs has finally been provided by Wang et al (12) in this issue of the Journal. These investigators found that the methylation levels of both genomic DNA (gDNA) and long interspersed nucleotide element-1 (LINE-1), a retro-transposon whose expression is closely regulated by epigenetic mechanisms, were decreased in neural tissues from NTD cases relative to unaffected control tissues. LINE-1 elements comprise a significant portion of the human genome and are typically silenced by hypermethylation during early development (13). In studying a high-NTD-risk population from an environmentally compromised region of China, the investigators hoped to link altered one-carbon metabolism with embryonic methylation status to the risk of an adverse pregnancy outcome. With a limited cohort of 48 NTD cases, including 27 anterior (anencephalics and encephaloceles), 21 cases of spina bifida, and 49 controls (pregnancies terminated for reasons other than the presence of congenital malformations), they found that gDNA from neural tissues of the anterior NTD cases had the lowest levels of global methylation, followed by posterior NTD cases and then controls. The relation between methylation status and maternal plasma concentrations of folate and vitamin B-12 failed to hold up in cases in comparison with controls, with only vitamin B-12 concentrations being significantly lower in the case mothers.

The study is an important first effort in understanding the importance of epigenetic factors and one-carbon metabolism in the etiology of complex birth defects. Although far from perfect, the study raises some important questions. First among these is understanding the causes of global hypomethylation in environmentally compromised areas. Whereas nutritional factors on the surface would appear to be paramount, it is highly likely that the exposure to heavy metals such as arsenic and cadmium and air particulates could trigger developmental changes that are manifest epigenetically. With the advent of newer methylation assays will come a greater understanding of the association between impaired DNA methylation and NTD etiology in humans and will probably allow us to identify new genes essential for normal neural tube closure.

The authors had no conflicts of interest with respect to the issues raised in this editorial.

REFERENCES