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RESEARCH NEWS

Genetic Predisposition to Neural Tube Defects?

A review of: Christensen B, Arbour L, Tran P, *et al*. 1999 Genetic polymorphisms in methylenetetrahydrofolate reductase and methionine synthase, folate levels in red blood cells, and risk of neural tube defects. Am J Med Genet 84:151–157.

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Research in the last few years now suggests that the "thermolabile" methylene tetrahydrofolate reductase (MTHFR) associated C677T polymorphism leads to an increased risk of offspring with neural tube defects (NTDs). In a study of 56 Canadian patients with spina bifida, 62 mothers of patients, 97 children without NTDs (controls) and 90 mothers of controls, Christensen *et al*. (1) observed that 18–20% of patients with NTDs and their mothers were homozygous for the C677T MTHFR polymorphism, compared to 11% for controls and control mothers, implying an increased risk of NTD associated with the "thermolabile" MTHFR polymorphism. Having an RBC folate concentration in the lowest quartile, in conjunction with homozygosity for the C677T polymorphism, further enhanced risk for NTDs, providing evidence for a "genetic-nutrient" interaction in risk association for NTDs. In the Irish, Shields and coworkers (2) produced data that led to similar conclusions. However, their patient population (n=271 NTD cases and n=218 NTD family members, predominantly parents) was considerably larger, providing enhanced statistical significance. These investigators detected the homozygous C677T MTHFR polymorphism in 19% of NTD cases vs. 8% of controls ($p=0.0005$), indicating that the homozygous MTHFR polymorphism was a key genetic determinant in MTHFR-derived NTD risk. These authors correctly noted that the majority of NTDs, even those which may be potentially preventable by folate therapy, must be associated with factors unrelated to MTHFR since most C677T homozygotes do not have NTDs (suggesting low penetrance of the MTHFR polymorphism as a risk factor for NTDs, or perhaps adequate folic acid intake), and most women carrying fetuses with NTDs do not manifest clinically deficient folate levels in plasma or RBCs (although this does not preclude the possibility that affected fetuses may have a biochemical abnormality requiring higher folic acid concentrations themselves). Data that conflicted with these conclusions were presented from a study of South African Blacks by Ubbink *et al*. (3). Folate, homocysteine (HCys) levels, and presence of the "thermolabile" MTHFR polymorphism, were determined in 107 healthy rural black women, 54 rural black women with a history of pregnancy complicated by NTDs, and 101 apparently healthy urban black women. Ubbink *et al*. (3) found that homozygosity for the "thermolabile" MTHFR polymorphism did not contribute a genetic risk factor for NTDs in this population; moreover, no abnormality in HCys metabolism was detected in women with NTD affected pregnancies although they may have had higher plasma folic acid levels.

Although controversial, the emerging model features a "genetic-nutrient" interaction leading to increased risk for NTDs. Maternal hyperhomocysteinemia (with or without the C677T allele) has been associated with increased risk of NTD in the fetus; "thermolabile" MTHFR homozygotes are at risk of hyperhomocysteinemia when plasma folate is decreased, and decreased MTHFR activity may further depress already low folate concentrations. As observed by Shields *et al*. (2), consensus may only come with studies of much larger mother-child pairs associated with NTDs, or through application of transmission disequilibrium tests (TDT) to three-generation families to include MTHFR heterozygous maternal grandparents of NTD offspring. Clearly, we have a lot to learn about the role of folic acid, and the enzymes responsible for its metabolism, in human embryogenesis and development.

1. Christensen B, Arbour L, Tran P, Leclerc D, Sabbaghian N, Platt R, Gilfix BM, Rosenblatt DS, Gravel RA, Forbes P, Rozen R 1999 Genetic polymorphisms in ethylenetetrahydrofolate reductase and methionine synthase, folate levels in red blood cells, and risk of neural tube defects. Am J Med Genet 84:151–157
2. Shields DC, Kirke PN, Mills JL, Ramsbottom D, Molloy AM, Burke H, Weir DG, Scott JM, Whitehead AS 1999 The "thermolabile" variant of methylenetetrahydrofolate reductase and neural tube defects: an evaluation of genetic risk and the relative importance of the genotypes of the embryo and the mother. Am J Hum Genet 64:1045–1055
3. Ubbink JB, Christianson A, Bester MJ, Van Allen MI, Venter PA, Delport R, Blom HJ, van der Merwe A, Potgieter H, Hayward Vermaak WJ 1999 Folate status, homocystein metabolism, and methylene tetrahydrofolate reductase genotype in rural south African Blacks with a history of pregnancy complicated by neural tube defects. Metabolism 48:269–274

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