

Folate, the methionine cycle, and Alzheimer's disease

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“Folate... its not just for women anymore!” This was the witty comment made by one of my (female) administrators several years ago after viewing my presentation about the role of folate deficiency in Alzheimer's disease. For those of you who may not be aware, this statement was both a take-off of a current US television advertisement having nothing to do with folate or nutrition, coupled with the extent of common knowledge back then: i.e., that folate was very important for women during pregnancy for proper fetal development. And, indeed, that was about it, or so we thought back then.

Alzheimer's disease has a multifactorial etiology, encompassing genetic and nutritional risk factors, and no single risk factor can account for all cases. So where does that leave us? Perhaps with the realization that clinical manifestation of Alzheimer's disease may derive from, and perhaps more importantly be obligatorily dependent upon, the convergence of two or more risk factors. Herein lies at least one difficulty: A genetic predisposition may remain latent pending an age-related critical decline in nutrition. This has confounded the linkage of nutrition to Alzheimer's disease, since contributing nutritional deficiencies may remain undetected, and, even if considered, may not receive sufficient attention if they are benign in isolation.

Ironically, Reye-Engel and colleagues [3] demonstrate that the now-routine prevention of overt developmental abnormalities by bolstering consumption of folate during pregnancy has fostered a marked increase in (phenotypically) normal individuals that carry deficient polymorphisms in methylene tetra-hydrofolate

reductase (which utilizes folate to remethylate homocysteine). This transient nutritional supplementation may therefore actually increase the number of individuals harboring a latent genetic risk towards Alzheimer's disease that may manifest late in life, especially when coupled with an age-related decline in folate consumption.

I recall the first time I applied for funding in this area to the Alzheimer's Association in the late 90's. I proposed to investigate potentiation by folate deficiency of genetic predisposition to Alzheimer's disease. One of the reviewers stated, “There is no evidence that folate deprivation has anything to do with Alzheimer's disease.” I kept at it, however, and revised and resubmitted. . . twice. . . Some three years later, the third submission of this twice-modified grant proposal was met with the comment “Everyone knows that folate deficiency promotes Alzheimer's disease.” This was just one reflection of how fast our knowledge advanced on the impact of nutritional deficiencies on neurodegeneration. Yet, even while folate deficiency and increased homocysteine have become recognized as cofactors in the onset and progression of Alzheimer's disease, further intricacies of the impact of perturbations in the methionine cycle on Alzheimer's disease continue to be reported. Recent findings from Scarpa and colleagues and our own laboratory demonstrate that a deficiency in S-adenosyl methionine (SAM or “S-AMe”), which rapidly declines as a consequence of dietary or genetic folate deficiency, fosters overexpression of otherwise normal presenilin-1, leading to increased gamma-secretase activity and A β generation [2], virtually crippling

ples glutathione-mediated quenching of reactive oxygen species in brain [4], and reduces acetylcholine synthesis [1]. The good news is that these same studies demonstrate that dietary supplementation with SAM can attenuate the consequences of both dietary and genetically-induced folate deprivation. . . a combinatorial approach to dietary supplementation, coupled with a good diet itself, is likely to provide maximal neuroprotection as we age.

The articles contained within this special issue of the Journal of Alzheimer's disease, generously contributed by a number of experts in this field, explore prior and novel means by which folate deficiency and perturbations of the methionine cycle impact age-related neuronal cognition. . . "Food for thought" about food for thought.

References

- [1] A. Chan, F. Tchantchou, V. Graves, R. Rozen and T.B. Shea, Dietary and genetic compromise in folate availability reduces acetylcholine, cognitive performance and increases aggression, *Proc Int Alz Ass* (2006), in press.
- [2] A. Fusco, L. Seminara, R.A. Cavallaro, F. D'Anselmi and S. Scarpa, S-adenosylmethionine/homocysteine cycle alterations modify DNA methylation status with consequent deregulation of PS1 and BACE and beta-amyloid production, *Mol Cell Neurosci* **28** (2005), 195–204.
- [3] A. Reyes-Engel, E. Munoz, M.J. Gaitan, E. Fabre, M. Gallo, J.L. Dieguez, M. Ruiz and M. Morell, Implications on human fertility of the 677C->T and 1298A->C polymorphisms of the MTHFR gene: consequences of a possible genetic selection, *Mol Hum Reprod* **8** (2002), 952–957.
- [4] F. Tchantchou, M. Graves, D. Ortiz and T.B. Shea, S-adenosyl methionine: a link between nutritional and genetic risk factors in Alzheimer's disease, *J Nutri Health Aging* (2005), in press.