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Editorial

Has Prenatal Folate Supplementation Established an At-Risk Population for Age-Related Cognitive Decline?

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Abstract. Nutrition exerts a pervasive impact on normal and pathological conditions of the nervous system throughout life. Maternal folate supplementation during pregnancy has reduced developmental disorders of the nervous system, but may have also fostered an increase in individuals harboring genetic polymorphisms that compromise folate usage. Such individuals may harbor a lifetime requirement for additional dietary folate, often not met beyond peri/postnatal periods. An increased association of such polymorphisms has been detected in individuals with autism. Prenatal nutritional supplementation may have inadvertently established latent conditions that, in the absence of continued supplementation, may lead to age-related cognitive decline.

Keywords: Dementia, genetic risk, methylene tetrahydrofolate reductase, nutrition, polymorphism, prenatal

Inadequate maternal folate during pregnancy increases developmental abnormalities of the fetal nervous system. Folate deficiency has also been associated with autism and epilepsy in youth, depression, and schizophrenia in adults, and neurodegenerative conditions such as Alzheimer's disease (AD), Parkinson's disease, amyotrophic lateral sclerosis, and stroke in the elderly [1–4].

Folate plays a critical role in one-carbon metabolism, in which folate and B12 convert homocysteine to methionine, which generates S-adenosylmethionine (SAM), the major methyl donor. The C677T polymorphism of 5′-methylene tetrahydrofolate reductase (MTHFR; a key enzyme required to activate folate for methylation), displays reduced activity. This polymorphism is associated with impaired DNA methylation [5]. Folate deficiency compromises SAM-dependent histone methylation [6]. Compromised histone methylation is associated with a wide range of neurological disorders, including impaired learning and memory, intellectual disability, addiction, schizophrenia, autism, depression, and neurodegeneration [4, 7, 8].

Compromise of the one-carbon metabolism can accompany, and may be causal to, neurodegeneration in AD [9]. S-adenosylhomocysteine (SAH), the downstream product resulting from SAM-mediated transmethylation reactions, is elevated in brains of individuals with AD; SAH competitively inhibits SAM-dependent reactions, further reducing methylation in AD [10]. In this regard, the activity of the enzyme responsible for its generation (methionine-S-adenosyltransferase) is decreased in the spinal fluid and

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brains of individuals exhibiting neurodegeneration [10, 11]. Resultant impaired methylation likely potentiates aberrant gene expression, leading to increased generation of amyloid-β (Aβ). Oxidative damage resulting from increased Aβ may derive from aberrant expression of AD-related genes as a consequence of impaired methylation [12]. These findings were augmented by studies in transgenic mice, in which impaired DNA methylation resulted in overexpression of presenilin-1, β-secretase, and γ-secretase, which was accompanied by cognitive decline, reduced acetylcholine levels, and accumulation of intracellular and extracellular Aβ and phospho-tau [9, 13–15].

Recognition of the association of folate insufficiency with developmental defects fostered increased consumption of folate-rich foods during pregnancy over the last 20 years, which significantly reduced these developmental problems [16, 17]. Since maternal folate supplementation can mask the adverse effects of impaired fetal MTHFR enzymatic activity during pregnancy, prenatal and perinatal supplementation may therefore have increased survival rates of infants possessing the C677T MTHFR polymorphism via reduction in miscarriage rates. The C677T MTHFR polymorphism has increased by 24% in individuals born during the period from 1976–2001; older age groups displayed no change [18]. Prenatal folate supplementation may therefore have fostered the birth of a substantial cohort of individuals harboring genetic deficiency in folate metabolism [19].

While folate supplementation could compensate for MTHFR deficiency throughout life [20], nutrition unfortunately declines with age, and even more so in AD [21, 22]. When such an individual's diet is no longer adequately supplemented, a deficiency in MTHFR may present one the above clinical conditions that can stem from impairment in one-carbon metabolism. In this regard, the C677T polymorphism has already been found in significantly higher frequency in individuals with autism, and this increased frequency correlates with the onset of maternal folate supplementation during pregnancy [19, 23–25]. The number of individuals for whom folate supplementation will be critical to avoid dementia may have increased in parallel; notably, since AD is confined to aged individuals, it remains to be seen whether or not any such increased latent risk exists. Notably, MTHFR polymorphisms, including 677T, are indeed more prevalent in individuals with AD than in non-demented individuals [26–29], confirming that genetic MTHFR compromise can contribute to AD. An additional study has linked the 677T polymorphism with mild cognitive impairment [30]. Moreover, the C677T polymorphism was not associated with impaired cognition or depression in adult humans receiving with adequate folate levels [20], supporting the notion that supplementation can offset this genetic compromise. The characteristic impaired cognitive performance, diminished neurotransmitter levels, and increased oxidative damage in MTHFR ± mice were alleviated by dietary supplementation with folate or SAM [15].

As evidence mounts that optimized nutrition, including supplementation, can modulate cognitive decline in dementia, one can hope for a decrease in the incidence of AD [31–33]. However, the considerations presented herein prompt the speculation that maternal folate supplementation may, as offspring of mothers receiving supplementation age, also give rise to an increased population of individuals with a latent genetic predisposition for age-related cognitive impairment. Similar speculation may hold true for additional polymorphisms of other enzymes that regulate different metabolic pathways. Supportive animal studies to determine whether or not prenatal supplementation can lead to age-related cognitive decline would be of interest.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2170).

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