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EXPLORING NOVEL TREATMENT OPTIONS: *COGNITIVE DECLINE IN ALZHEIMER'S DISEASE*

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ABSTRACT

Alzheimer's disease (AD) and dementia have enormous financial and social impacts on society. It is predicted that almost 36 million people will have dementia in 2010, a figure which is anticipated to double every 20 years as the world population ages. Prevention of AD or slowing of the progression of AD would provide significant benefits. There are multiple ways in which vitamin B_{12}, vitamin B_6, folate, and homocysteine (Hcy) play a role in the pathogenesis of AD. Vitamin B_{12}, vitamin B_6, and folate deficiencies are associated with various cognitive disorders, including dementia. Neuroinflammatory oxidative stress occurs early in AD pathology. Total blood Hcy levels are utilized as a marker to assist in diagnosing such deficiencies. Hcy contributes to pathological cascades involving amyloid plaques and neurofibrillary tangles (NFTs). This review provides a thorough description of several factors involved in the development of the pathological changes associated with AD, such as neuroinflammatory oxidative stress and methylation, apoptosis, NFTs, amyloid plaques, and cerebrospinal fluid biomarkers. The review also considers the rationale for a combined B-vitamin and antioxidant supplement (Cerefolin NAC) in treating and slowing AD-related cognitive decline.

In this Expert Review Supplement, Andrew McCaddon, MD, and Peter R. Hudson, PhD provide a comprehensive review of factors involved in AD pathology as well as evidence supporting the use of a combined B-vitamin and antioxidant supplement (Cerefolin NAC) for AD-related cognitive decline. A commentary on this article is provided by leading AD expert Jeffrey L. Cummings, MD.

L-METHYLFOLATE, METHYLCOBALAMIN, AND *N*-ACETYLCYSTEINE IN THE TREATMENT OF ALZHEIMER'S DISEASE–RELATED COGNITIVE DECLINE

By Andrew McCaddon, MD, and Peter R. Hudson, PhD

Introduction

Almost 36 million people will have dementia in 2010—an alarming figure set to double every 20 years with the "greying" of the world population.[1] Alzheimer's disease (AD) and dementia have enormous financial and social impacts on society. Prevention or illness delay of even a small percentage of cases would provide significant cost benefits for health-care systems.[2] This review considers the rationale for a combined B-vitamin and antioxidant supplement (Cerefolin NAC) in treating and slowing AD-related cognitive decline.

B-Vitamins and Dementia

Vitamin B_{12} and folate deficiencies are associated with various cognitive disorders, including dementia.[3] In the 1980s, plasma total homocysteine (tHcy) assays were introduced to assist in diagnosing these deficiencies. Hcy is derived from dietary methionine. Cells re-methylate Hcy to methionine using B_{12}-dependent methionine synthase; 5-methyltetrahydrofolate (5-MTHF) acts as a methyl donor (Figure 1A). Alternatively, Hcy is converted to cystathionine, and ultimately cysteine, by B_6-dependent cystathionine β-synthase. Blood Hcy levels rise in B_6, B_{12}, and folate deficiencies.Higher levels are also associated with aging, smoking, male gender, renal impairment, and drugs including methotrexate, metformin, and levodopa.[4]

Using tHcy as a marker, B vitamin deficiencies were found to be highly prevalent in the elderly.[5,6] This led to speculation that elevated blood Hcy, hyperhomocysteinemia, might occur commonly in dementias, including AD.[7-9] Hyperhomocysteinemia implies impaired methylation reactions (hypomethylation),[10] with predictable adverse effects for neurotransmitter synthesis and AD neuropathology. Hcy is also associated with vascular disease,[11] itself a risk factor for dementia.[12]

Evidence for the "homocysteine hypothesis of dementia" came with reports of hyperhomocysteinemia in patients with clinically and pathologically confirmed AD.[13,14] Raised blood levels were also observed in mild cognitive impairment (MCI) and vascular dementia.[15,16] Although elevated Hcy could be a consequence of, or coincidental with, dementia it is now recognized to be associated with an increased risk for both cognitive decline and incident dementia.[17-19]

One curious feature of the relationship of Hcy with dementia is the absence of macrocytic anemia.[20,21] The relationship is also independent of nutritional status,[13,22] suggesting that rather than arising from dietary deficiency or malabsorption, it may reflect effects of oxidative stress on Hcy metabolism.[23,24]

Oxidative Damage,"Neuroinflammation," and AD

Oxidative damage is a prominent feature of AD.[25] Lipid peroxidation and levels of protein and nucleic acid oxidation are significantly increased in vulnerable brain regions.[26] Such damage is not confined to AD, but also occurs in patients with amnestic MCI.[27]

There is also an association between AD and inflammation.[28] Epidemiological studies link the use of anti-inflammatory drugs with a reduced risk for AD and expression of inflammatory mediators is increased in postmortem AD brains.[29] Such "neuroinflammation" is likely a major driving force in the disease. Rather than being the primary lesion in AD, amyloid plaques and neurofibrillary tangles may be compensatory phenomena, ie, end-stage manifestations of cellular adaptation preceded by elevated markers of oxidative stress.[30]

Oxidative Stress and Methylation

Recycling of Hcy to methionine by methionine synthase (MS) requires vitamin B_{12} as co-factor and 5-MTHF as methyl donor (Figure 1A). Methionine adenosyltransferase then converts methionine to S-adenosylmethionine (SAM)—a substrate for multitudinous cellular methylation reactions.

SAM synthesis is impaired by oxidative stress; cob(I)alamin, an intermediate in the MS reaction, is vulnerable to oxidative deactivation to cob(II)alamin.[31] Reductive re-methylation of cob(II)alamin requires a methyl group donated by SAM itself. Oxidatively impaired MS activity also depletes folate stores via reduced polyglutamation—an essential prerequisite for cellular folate retention.[32]

Oxidative stress increases the requirement for, but decreases synthesis of, SAM.[23] Naturally, an auto-corrective mechanism exists. Hepatic Hcy is metabolized via the transsulphuration pathway, culminating in synthesis of glutathione—an essential antioxidant for intracellular redox homeostasis.[4] Neurones and other central nervous system (CNS) cells do not fully express this pathway, nor does brain tissue possess an alternative pathway for re-methylating Hcy.[33] Hence, its capacity to metabolize Hcy is extremely vulnerable to oxidative stress and dependent on an adequate supply of folate and B_{12}.

Oxidative Stress and Mitochondrial Dysfunction

Mitochondria are pivotal in cell life and death, producing energy in the form of adenosine triphosphate (ATP) and sequestering calcium, but also generating free radicals and serving as repositories for proteins regulating apoptosis. Perturbations in their function sensitize cells to neurotoxic insults and may initiate cell death.[34] Alterations in energy metabolism occur early in AD. Energy consumption is drastically decreased in cortical and hippocampal regions, implying compromised mitochondrial function. This is accompanied by elevated reactive oxygen species (ROS), contributing to increased neuronal loss.[35] One potential mechanism is the binding of amyloid-beta (Aβ) with mitochondrial membrane proteins involved in adenosine diphosphate (ADP)/ATP transfer.[36]

Other processes can influence mitochondrial bioenergetics. Succinyl-CoA is an essential component of the mitochondrial citric acid cycle, which generates ATP via the mitochondrial electron-transport chain. One route of synthesis is from α-ketoglutarate via the enzyme complex, β-ketoglutarate dehydrogenase. Oxidative stress can impair this complex, compromising energy metabolism and further enhancing ROS formation in AD and other neurodegenerative diseases.[37]

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Succinyl-CoA is also synthesised from methylmalonyl-CoA via vitamin B_{12}-dependent methylmalonyl-CoA mutase.[38] While inhibition of this enzyme by ROS is still being investigated,[39] B_{12} deficiency causes accumulation of methylmalonic acid (MMA). Evidence from the disorder methylmalonic aciduria suggests that neurodegeneration is associated with inhibition of the respiratory chain and tricarboxylic acid cycle not by MMA alone, but by synergistically acting alternative metabolites, in particular 2-methylcitric acid, malonic acid, and propionyl-CoA.[40] Of relevance, a study of healthy elderly individuals showed a high prevalence of metabolically significant vitamin B_{12} deficiency, with increased MMA being associated with lower cognitive function scores.[41]

A potentially prudent strategy for maximal protection against these adverse metabolic insults upon mitochondria, and on energy production via the tricarboxylic acid cycle and electron transport chain, is to optimize both glutathione synthesis and vitamin B_{12} status.

Relationship Between Hcy, Hypomethylation, and AD Pathology

AD is characterized by intraneuronal neurofibrillary tangles and extracellular amyloid plaques. Hyperhomocysteinemia and hypomethylation influence the development of these lesions.

Neurofibrillary Tangle Formation

Neurofibrillary tangles (NFTs) are formed by the microtubule-associated protein tau. Tau is modulated by phosphorylation; the ability of tau to bind to and stabilize microtubules correlates inversely with its phosphorylation.[42] Tau is highly phosphorylated in AD and other "tauopathies." Disordered phosphorylation disrupts the normal co-localization of tau with microtubules, leading to hyperphosphorylation, tau-tau interactions, paired helical filaments, and ultimately aggregation into NFTs.[43]

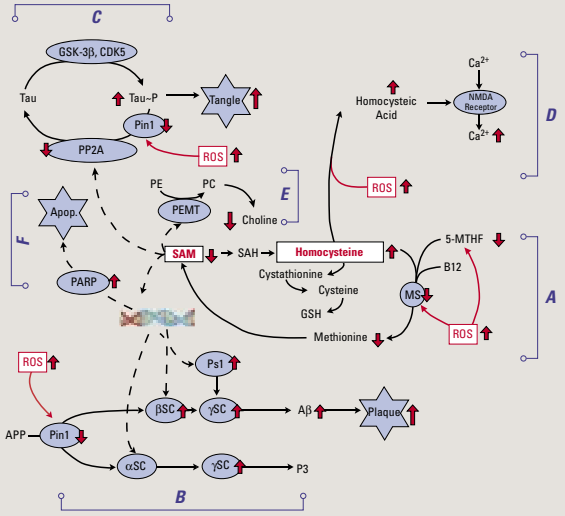
Tau phosphorylation is regulated by competing effects of kinases and phosphatases; attention has focused on the kinases GSK3β and CDK5 and the phosphatase PP2A. PP2A actively dephosphorylates abnormal tau.[44]

PP2A comprises regulatory and catalytic subunits; methylation of the latter is critical, suggesting that hypomethylation leads to tau hyperphosphorylation (Figure 1C).[45] There is a negative correlation between phosphorylated tau and markers of methylation status in cerebrospinal fluid (CSF) of patients with various neurological disorders, including AD.[46] Impaired folate and methylation status is closely linked to NFT formation,[47,48] but preventable by supplementation in animal models.[49,50] Interestingly, a recent study has also shown that GSK3β activity is increased in mice reared on a B-vitamin–deficient diet.[51] The authors also confirmed previous reports of decreased substrate specificity for PP2A in folate deficient mice.

Pin1 is another important tau regulatory enzyme. It ensures that phosphorylated-tau is in the correct conformation for de-phosphorylation by PP2A.[52] However, Pin1 is downregulated and oxidized in MCI and AD hippocampus, providing further evidence linking oxidative damage and NFT formation.[53]

FIGURE

Role of Folate Depletion and Oxidative Downregulation of the B_{12}-Dependent Methionine Synthase Reaction in the Development of Pathological Changes in Alzheimer's Disease



A: *Homocysteine remethylation.* 5-MTHF=5-methyltetrahydrofolate, ROS=reactive oxidative species, in particular O_2, the superoxide free radical, MS=methionine synthase, SAM=S-adenosyl methonine, SAH=S-adenosyl homocysteine.
B: *Amyloid-β production.* APP=amyloid precursor protein, Pin1=peptidyl-propyl cis/trans-isomerase, αSC=α-secretase, βSC=β-secretase, γSC=γ-secretase, Ps1=pre-senilin-1, Aβ=amyloid-β, p3=p3 peptide (Aβ peptide residues 17-40/42).
C: *Tau de-phosphorylation.* PP2A=protein phosphatase 2A, GSK-3β=glycogen synthase kinase 3β, CDK5=cyclin-dependent kinase-5.
D: *NMDA receptor.* Ca^{2+}=calcium flux through the NMDA glutamate receptor.
E: *Choline biosynthesis.* PEMT=phosphatidyl-ethanolamine methyl transferases, PE=phosphatidyl-ethanolamine, PC=phosphatidyl-choline.
F: *PARP activation and apoptosis.* PARP=poly (ADP-ribose) polymerase.

Small arrows=the effect of oxidative stress/methylation on enzyme activity or cellular levels of a substance. Red arrows=an effect mediated by oxidative stress. Black dotted arrows=an effect mediated by hypomethylation.

Amyloid Plaque Formation

Amyloid precursor protein (APP) is cleaved by α, β, and γ secretases (Figure 1B). Normally, APP is cleaved by α-secretase, releasing an N-terminal fragment, sAPPα. sAPPα is neuroprotective, participating in synapse formation and integrity of memory.[54,55] Alternative cleavage of APP by β-secretase generates a secreted APP β peptide, sAPPβ. Cleavage by γ-secretase of the remaining C-terminal end of APP leads to formation of Aβ peptide, comprising 39-43 amino acids, depending on the precise cleavage site. Aβ peptides subsequently aggregate into harmful amyloid plaques (AP).[56]

Similar to tau, Pin1 maintains APP in a configuration that reduces its metabolism by β-secretase, shifting cellular selectivity towards non-amyloidogenic APP processing.[57] Thus, oxidative downregulation of Pin1 adversely influences Aβ formation and its subsequent aggregation into AP.[52,58]

Hypomethylation also contributes to Aβ production. The pathway for APP processing into Aβ involves β-secretase and γ–secretase activity. The γ–secretase complex comprises four individual proteins: presenilin (PS1), nicastrin, APH-1, and PEN-2.[59] PS1 is the catalytic subunit, and mutations in its gene are a risk factor for AD.[60]

The expression of β-secretase and PS1 are downregulated by DNA methylation. In vitro, deficiency of folate and vitamin B_{12} in cell culture medium reduces SAM levels with a consequent increase in PS1 and β-secretase levels and increased Aβ production. Adding SAM to deficient medium restores normal gene expression and reduces Aβ levels.[61] In vivo, folate deficient mice show increased APP phosphorylation in association with the expected changes in methylation in brain tissue.[48] Similarly, hyperhomocysteinemic rats have elevated PS1 and a prominent spatial memory deficit which is reversible by folate and B_{12} supplementation.[62] Elevated Hcy also augments the neurotoxicity of Aβ, at least in vitro, by potentiating oxidative stress.[63]

CSF Biomarkers in AD and MCI

There is evidence for the inter-relationships between Hcy, Aβ, tau, and oxidative stress in CSF. CSF levels of Aβ and tau are associated with progression from MCI to AD.[64-67] The association between CSF phospho-tau and Hcy in AD suggests that hypomethylation links hyperhomocysteinemia and neurodegeneration.[68,46] Oxidative stress markers, namely lipid peroxidation products (isoprostanes), accompany increases in Aβ, tau, and Hcy. CSF Aβ and isoprostane levels are probably the earliest markers for neuronal damage in AD.[69] Brain tissue studies show that other lipid peroxidation products (4-hydroxynonenal and acrolein) are increased in

selected regions of patients with MCI, suggesting that lipid peroxidation occurs early in AD pathogenesis.[70]

Neurochemistry

AD is characterized by deficits in the cholinergic neurotransmitter system, although there are also deficiencies in other neurotransmitter systems.[71] Glutamate is an excitatory amino acid involved in cortico-cortical association pathways. The *N*-methyl-D-aspartate (NMDA) receptor is a marker for glutamate activity. NMDA receptors are present in high density in the cortex and hippocampus and play an important role in learning and memory.[72] Elevated levels of oxidised Hcy derivatives and limited SAM availability due to vitamin B_{12} and folate deficiencies might adversely affect both glutamatergic and cholinergic systems.[7]

Glutamatergic

The NMDA receptor complex is a large protein assembly with different binding sites for different ligands, including an NMDA site, a strychnine insensitive glycine-binding site, and a binding site for non-competitive antagonists. Homocysteic acid and homocysteine sulphinic acid are oxidized derivatives of Hcy, and exert toxic effects on NMDA receptors (Figure 1D). These metabolites are 250-fold more efficient in disrupting neuronal networks than Hcy itself, and cause excess calcium influx, free-radical generation, collapse of the mitochondrial membrane potential and, eventually, neuronal death.[73,74]

Cholinergic

Neuronal choline is derived from intrasynaptic choline (via degradation of acetylcholine by acetylcholinesterase), extracellular choline (via a low affinity transport mechanism), and intraneuronal choline (via sequential methylation of membrane phosphatidylethanolamine [PE]).[75] Intraneuronal choline will be depleted if SAM availability is limited[7] (Figure 1E). Impaired MS activity also induces the hepatic B_{12}-independent betaine homocysteine methyltransferase pathway, betaine supplying a methyl group instead of methylfolate.[76] Since betaine is derived from choline oxidation, this will reduce extraneuronal choline supplies.[7]

Impaired PE methylation also influences transmembrane signal transmission. PE largely faces the cytoplasm, whereas phosphatidylcholine faces the extracellular space. The methylating enzymes (PEMT 1 and 2) are also asymmetrically distributed. Phospholipid methylation commences on the cytoplasmic side of the membrane and methylated phospholipids are translocated to the exterior. This increases membrane fluidity, and is coupled to calcium influx and release of intracellular secondary messengers.[77]

PARP Activation, DNA Repair, and Apoptosis

Gene expression is partly attenuated by methylated DNA stretches—CpG islands. Hypomethylation induces gene transcription and DNA strand breakage.[78,79] In cultured neurones, Hcy itself induces breakages,[80] probably via free-radical induced damage. In vivo, decreased thymidylate synthesis with subsequent uracil misincorporation into DNA probably also contributes.[81] Uracil is excised from DNA, generating transient breaks requiring repair. Poly (ADP-ribose) polymerase (PARP) recognizes damaged DNA and prepares it for repair. However, with excessive damage, PARP triggers a cascade of events leading to cell death.[82] PARP-controlled cell death is the major pathway for neuronal apoptosis. Hence, hypomethylation is closely linked with neuronal apoptosis (Figure 1F).

Cerebral Ischemia, Atrophy, and Blood Brain Barrier Abnormalities

Elevated Hcy is a risk factor for atherothrombotic disease, and folate supplementation is effective in secondary stroke prevention.[83] AD commonly co-occurs with stroke, suggesting that hyperhomocysteinaemia and AD might also be partly linked via micro-vascular disease.[84] Elevated Hcy is also associated with brain atrophy[85,86] and blood-brain barrier (BBB) dysfunction,[87] which is reversible by high-dose B-vitamin supplementation.[88]

Method of Action of Cerefolin NAC

Treatments for AD include cholinesterase inhibitors and the NMDA receptor antagonist memantine,[89] although these are only indicated for patients with established disease. Cerefolin NAC provides a unique option in early AD and MCI by addressing inter-related mechanisms associated with oxidative stress and B-vitamin deficiency (Figure 1). Open-label trials adopting a similar synergistic approach show considerable promise in early[90] and late-stage AD.[91]

Unlike other folate supplements which contain synthetic folic acid, Cerefolin NAC contains the naturally occurring 5-MTHF (5.6 mg). This has an important advantage over folic acid. Folic acid can inhibit transport of 5-MTHF across the BBB.[92] Hence, an accumulation of unmetabolized folic acid resulting from the use of alternative supplements might actually be detrimental in treating CNS disorders.

Cerefolin NAC also comprises *N*-acetylcysteine (NAC) (600 mg)—a membrane-permeable cysteine precursor rapidly hydrolyzed intracellularly to cysteine, a precursor of glutathione (GSH). Cysteine availability is the rate-limiting step in GSH synthesis. GSH is a major component of pathways protecting cells from oxidative stress and apoptosis. Other commonly used antioxidants, including vitamin C, vitamin K, and lipoic acid, neutralize free radicals but cannot replenish cysteine required for GSH synthesis.[93] NAC itself is also an antioxidant and free-radical scavenger, and can additionally lower Hcy levels by increasing urinary excretion.[94] In a double-blind trial of patients with probable AD, NAC improved nearly every outcome measure, although significant differences were obtained only for a subset of cognitive tasks.[95]

The third component of Cerefolin NAC is methylcobalamin (2 mg)—the co-factor for MS in the conversion of Hcy to methionine. High-dose oral vitamin B_{12} (1–2 mg/day) is as effective as intramuscular administration.[96] GSH is required for intracellular cobalamin processing.[23,97] Hence, Cerefolin NAC might have advantages over other methylcobalamin formulations. Cobalamin itself might also act as a ROS scavenger,[98] suppressing apoptosis and preventing cellular damage.[99,100]

Clinical Trials

Although Hcy-reducing clinical trials regarding dementia are disappointing, there are several important caveats.[101] Most trials to date are of insufficient size and short duration.[2] Also, lowering Hcy addresses only one of several pro-inflammatory mechanisms promoting oxidant stress and neurotoxicity. Completed trials have only included patients with mildly elevated Hcy levels; the role of Hcy reduction in patients with more robustly elevated levels for both primary prevention and therapeutic treatment of dementia remains unknown.

Nevertheless, a recent expert review concluded that folate, B_{12}, and Hcy levels should be determined in all dementia patients, and abnormal levels should be treated.[83] Substitution of these vitamins may also improve cognitive function in the absence of overt deficiency.[83] Given the close inter-dependent relationship between Hcy and oxidative stress, it is prudent to simultaneously administer antioxidants such as NAC when correcting such deficiencies. Several case studies, and two open-label studies, confirm the benefits of this synergistic approach.[102,103,90,91]

Summary

Neuroinflammatory oxidative stress occurs early in AD pathology. Elevated blood Hcy is a useful marker for such neuroinflammation.

Hcy contributes to pathological cascades involving AP and NFTs. In AD, Hcy should be lowered by B-vitamin supplements and NAC.

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QUESTION-AND-ANSWER SESSION

Q: Studies are showing that treatment initiated when pre-dementia or early memory loss is recognized leads to a better prognosis than waiting to initiate treatment once Alzheimer's disease (AD) or dementia is established. What options do clinicians have to address early memory loss?

Drs. McCaddon and Hudson: Clinical options for early memory loss comprise three broad categories: treating vascular risk factors, providing neuroprotection, and promoting neuronal reserves.[1] Vascular risk factors include hypertension, hypercholesterolemia, diabetes, smoking, and hyperhomocysteinemia, all of which should be actively screened for and addressed in all patients presenting with cognitive impairment. Neuroprotection includes ensuring adequate B_{12} and folate status, use of antioxidants, and addressing neuroinflammation. There is also evidence that neuronal reserves can be developed by encouraging cognitive, physical, and social activity.[1]

Q: Are there symptoms or markers that can be used to diagnose pre-dementia or early memory loss?

Drs. McCaddon and Hudson: There is a pathway of cognitive impairment where benign aging develops into mild cognitive impairment (MCI) and eventually AD. Early recognition of this trajectory is vital if the process is to be slowed or halted. Mitrushina and colleagues[2] reviewed neuropsychological tests used for the assessment of MCI and AD.[2] Many of these are time-consuming to perform and impractical in the busy physician's office. In addition, fatigue and sensory loss may impair the ability of the very elderly to complete these tests.[3] Milne and colleagues[4] reviewed shorter tests more suitable for use by the primary care physician, such as The General Practitioner Assessment of Cognition, the Memory Impairment Screen, and the Mini-Cognitive Assessment Instrument, and there is good agreement between these and the Mini-Mental State Examination.

Despite the wide variety of cognitive function tests available to the physician, anatomical and metabolic changes in the brain, demonstrated by magnetic resonance imaging and positron emission tomography, already occur $\geq$2 more years before a diagnosis of MCI can be made.[5,6] Biomarkers in cerebrospinal fluid, such as tau protein and amyloid-β, are promising candidates as early markers but await long-term studies of their potential clinical utility.[7] In summary, there are several techniques available to the physician for the detection of symptomatic MCI or AD. The detection of pre-clinical disease remains a challenge, but is a focus of much current research.

Q: What is your goal when treating patients with pre-dementia or early memory loss?

Drs. McCaddon and Hudson: The main goal is to delay or possibly even halt cognitive decline. Anything that might delay or prevent the onset of overt dementia would be beneficial from both an individual and epidemiological viewpoint. Remarkably, it is estimated that dementia prevalence would be halved if risk reduction strategies delayed the onset of dementia by only 5 years.[8]

Q: How important is safety and tolerability in a therapy used to address early memory loss?

Drs. McCaddon and Hudson: Safety and tolerability are extremely important in all patients, perhaps more so in those presenting with early memory loss. Cerefolin NAC is well tolerated and not associated with any significant drug interactions. It is also easy and convenient to use, being a single dose caplet with no necessary dose adjustment. In addition, in a recent cross-sectional study the relationship between folate and risk of cognitive impairment is reversed in patients with low B_{12}; high folate and low B_{12} concentrations are associated with an increased risk of cognitive impairment.[9] Although this association requires further investigation, Cerefolin NAC ensures that patients receive an optimal balance of the two vitamins.

Q: In your opinion, where does a novel therapy like Cerefolin NAC fit in the options available for memory loss?

Drs. McCaddon and Hudson: Cerefolin NAC is a useful option for early memory loss because it offers a synergistic approach to neuroprotection. A recent study confirmed that many patients with dementia have brain changes consistent with both AD and vascular dementia.[10] The authors suggested that it may be necessary to develop combination therapies to treat dementia. A similar synergistic approach should perhaps also be considered in patients presenting with early memory loss.

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COMMENTARY ON: *L-METHYLFOLATE, METHYLCOBALAMIN, AND N-ACETYLCYSTEINE IN THE TREATMENT OF ALZHEIMER'S DISEASE-RELATED COGNITIVE DECLINE*

By Jeffrey L. Cummings, MD

Drs. McCaddon and Hudson provide a thorough review of the multiple ways in which vitamin B_{12}, vitamin B_6, folate, and homocysteine (Hcy) are implicated in the pathogenesis of Alzheimer's disease (AD). They noted that Hcy is more often elevated in AD and in mild cognitive impairment (MCI) than in cognitively healthy elderly; phosphatases needed to limit tau hyperphosphorylation and neurofibrillary tangle formation require methylation and are dependent on folate and methylation status; cerebrospinal fluid (CSF) tau levels correlated with markers of methylation status; reduced folate and B_{12} levels lead to increase β-secretase and pesenilin 1 (PS1) actions leading to greater amyloid-β production in in vitro models; elevated Hcy levels in rats are associated with increased PS1 activity and spatial memory deficits that are reversed following treatment with B_{12} and folate; raised Hcy levels in vitro increase amyloid-β protein neurotoxicity; methylation impacts transmitters and transmitter function relevant to AD; in cultured neurons, Hcy induces injury in DNA and stimulates cell death pathways. B_{12} deficiency leads to accumulation of methyl malonic acid, which inhibits mitochondrial function and may compromise energy generation and impair maintenance of synaptic plasticity. Methylation abnormalities result in excessive generation of reactive oxygen species that contribute importantly to cell injury. Biomarkers of oxidative injury, such as isoprostanes, are elevated in AD and suggest excess oxidation. Thus, there are multiple pathways through which deficient methylation may contribute to AD. In some cases, the observations are derived from models with B_{12} or folate deficiency and some in vitro observations have not been tested in in vivo models. There are no biomarkers specific to some of the pathways implicated and the magnitude of the impact of the deficiency or its treatment has not been established for all the relationships. Two open-label experiments in early- and late-stage AD patients have suggested benefit.

Epidemiologic data support a role for Hcy elevation as a contributing factor to AD. Based on data from the Framingham study,[1] persons with elevated Hcy were at increased risk for developing AD; plasma levels >14 mmol/liter nearly doubled the risk of AD. In a consecutive series of 126 patients with AD, the patients were shown to have reduced CSF levels of L-methylfolate compared to healthy elderly controls.[2]

Double-blind, placebo-controlled trials support a role for folate supplementation in older persons with elevated levels of serum Hcy. Durga and colleagues[3] assigned 818 elderly individuals to 800 mcg of folic acid or placebo and treated them for 3 years. Subjects had 13–26 mmol/liter of Hcy at baseline. Those receiving folate supplementation performed better on tests of memory and sensory motor speed at the end of the trial. Patients had normal cognition at baseline. Aisen and colleagues[4] performed a randomized trial of folic acid 5 mg/day, vitamin B_{12} 1 mg/day, vitamin B_6 25 mg/day in patients with mild-to-moderate AD. Hcy levels declined significantly; there was no corresponding cognitive, functional, global, or behavioral benefit. Prespecified analyses of those with baseline Hcy levels in the highest quartile also showed no clinical benefit. The study shows that AD patients with normal levels are not improved by vitamin supplementation at these doses when used for 18 months and measured with standard clinical trial outcomes. Definitive conclusions about the utility of treatment of pathologically elevated Hcy levels awaits further study.

Cerefolin NAC, the compound described by Drs. McCaddon and Hudson, is available in the United States by prescription as a medical food. Medical foods are not supplements (which are taken by normal individuals, do not address a specific metabolic abnormality, and do not require a prescription) and they are not drugs (shown in rigorous double-blind, placebo-controlled trials to significantly improve a disease state). Medical foods address a specific metabolic condition associated with a disease state. Cerefolin NAC reduces hyerhomocysteinemia that has been associated with memory impairment, AD, and cerebrovascular disease. The package insert for Cerefolin NAC describes the intended treatment population as individuals under a physician's treatment for early memory loss with particular emphasis for those individuals diagnosed with or at risk for neurovascular oxidative stress and/or hyperhomocysteinemia, mild-to-moderate cognitive impairment with or without vitamin B_{12} deficiency, vascular dementia, or AD. Available data do not address all these conditions. The available data support use in older persons with elevated Hcy; studies in other populations are warranted. Cerefolin NAC is safe, with no important adverse events having been identified.

Cerefolin NAC is currently being studied in a double-blind, placebo-controlled trial to determine its effect on cognition and other biomarkers for patients with early memory loss. This study is being conducted at Rush University in Chicago and the results for the first phase (6-month data) are due in early 2010. The patients will continue in the study for 18 months.

Clinicians must base treatment recommendations on the available pathophysiological and epidemiologic studies until more definitive clinical trial data are available.

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