Addressing Cholinergic Deficits With Medical Foods

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ABSTRACT

Approximately 20% of adults aged 65-74 have mild cognitive impairment (MCI), a condition commonly leading to Alzheimer's disease (AD). An estimate 5.4 million Americans currently have AD, the prevalence of which is expected to more than double by 2050 (2011 Alzheimer's Disease Facts and Figures). The symptoms by which AD is commonly diagnosed reflect the disproportionate predominance of cholinergic nerve impairments that occur in the early stages (Pinto, Lanctot, and Herrmann). Prescription acetylcholinesterase inhibitors (AChEIs), which prolong the half-life of the cholinergic neurotransmitter acetylcholine (ACh), can effectively manage symptoms and slow disease progression for many AD patients. However, the effectiveness of AChEIs may be limited in the aging population. Age, gender, and genetic factors, as well as reduced food intake, dietary restrictions, and secondary health factors place these individuals at risk for nutritional deficiencies that can negatively impact cholinergic function and neurological health. Zymenta and Cerelist are medical foods that address these nutritional deficiencies by providing complementary ingredients to 1) support ACh synthesis; 2) reduce ACh breakdown; and 3) protect neuronal cell structure and function. This article reviews the health implications of a cholinergic deficit in patients with MCI as well as mild-to-moderate AD and describes how the ingredients in Zymenta and Cerelist provide an unique, integrative approach to the nutritional management of these dementias.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative condition that progressively robs individuals of their cognitive and functional capabilities and results in loss of independence and reduced quality of life. This devastating disease is projected to affect over 11 million Americans by 2050 (2011 Alzheimer's Disease Facts and Figures). Causative factors remain unclear and, lacking reliable clinical biomarkers, diagnosis is based on the presence of cognitive symptoms. However, neurodegenerative changes in the brain actually precede the onset of symptoms by a decade or more (Albert et al. 270-79). Thus, risk factor identification and early diagnosis and intervention may be keys for managing this disease.

The most established risk factor for AD, other than advanced age, is a family history of the disease, particularly among first-degree relatives (Green et al. 329-36). Another established risk factor for the development of AD is diagnosis of mild cognitive impairment (MCI), which is typified by cognitive impairments beyond those attributed to normal aging but do not significantly interfere with daily life. Because physiological changes in the brain actually begin years before symptoms of AD become evident, MCI may actually be the earliest symptomatic phase of AD onset. In fact, an expert panel recently defined "MCI due to AD" as the symptomatic predementia phase of AD and proposed guidance for identifying MCI due to AD from other forms of cognitive decline (Albert et al. 270-79). Progression to AD occurs much more rapidly in individuals with MCI than in cognitively-healthy adults. Among the 10-20% of adults over 65 years diagnosed with MCI, approximately half will be diagnosed with dementia, primarily AD, within the next three to four years according to the Alzheimer's facts and figures report (2011 Alzheimer's Disease Facts and Figures). While it is not clear why some patients with MCI progress to AD and others do not, a diagnosis of MCI may present a window of opportunity for early AD intervention.

Structural changes, such as development of beta-amyloid plaques, neurofibrillary tangles, and loss of neuronal cells, lead to alterations in neurotransmitter signaling and receptor binding affinity (Wollen 223-44). Localized inflammation and elevated reactive oxygen species promote the neurological changes that contribute to progressive mental decline. As no cure for AD exists, diagnosis is followed by years of progressive decline in mental and functional abilities.

Initial signs of MCI and early AD reflect the disproportionate targeting of cholinergic neuronal cells (Pinto, Lanctot, and Herrmann). Because cholinergic neurons innervate all areas of the brain, injury to these cells, and the consequent reduction in acetylcholine (ACh) levels, contribute to a diversity of symptoms, including cognitive and functional decline as well as behavioral and personality changes. Thus, early interventions that support cholinergic activity of the brain may help manage

symptoms and slow disease progression (Pinto, Lanctot, and Herrmann).

Zymenta and Cerelist are medical foods designed to offer nutritional support to maintain proper function of the cholinergic nervous system. These products provide nutrients that are essential for cholinergic activity and brain health but which are found to be lacking in the diets of up to 90% of American adults (Werder 159-95;Zeisel and da Costa 615-23). These nutritional deficiencies can exacerbate neurological impairments and minimize the therapeutic efficacy of treatments such as acetylcholinesterase inhibitors (AChEIs) (Werder 159-95;Zeisel and da Costa 615-23;Zeisel). By providing these nutrients in combination with other cholinergic-supporting ingredients, these products offer a multidimensional approach to managing cognitive changes that occur in the early stages of AD. This article explains the rationale behind Cerelist and Zymenta and summarizes how these products' ingredients offer cholinergic support for patients with MCI and mild-to-moderate AD.

Multiple approaches to cholinergic support

Supporting cholinergic health is a common goal in the treatment of MCI and early AD. Primary contributors to cholinergic dysfunction are reduced synthesis, increased degradation, and impaired signaling of ACh, a critical neurotransmitter in the brain that facilitates cognitive and functional activities. A common approach to medically managing cholinergic function involves AChEIs that inhibit the enzymatic breakdown of ACh, thereby prolonging its half-life. This is an effective means of managing AD progression, at least in the early stages (Pinto, Lanctot, and Herrmann;Wollen 223-44). Approximately 70% of neurologists routinely prescribe AChEIs to patients with MCI (Roberts et al. 425-31), a practice which has been shown to delay the progression from MCI to AD (Levey et al. 991-1001). However, the cholinergic benefits of AChEIs may be reduced or negated if ACh synthesis is low or receptor activity is impaired, resulting in disease progression. In addition to reducing the degradation of ACh, mechanisms of action that support its synthesis or increase receptor activity will help further support cholinergic function.

Extending the half-life of ACh, naturally

Medical management of early AD commonly involves use of pharmaceutical AChEIs such as tacrine, donepezil, galantamine, and rivastigmine. In fact, AChEIs are the most widely prescribed class of AD drugs in the United States (Wollen 223-44). In contrast to the relatively short history of use for pharmaceutically-derived AChEIs, plant-derived AChEIs such as the alkaloid Huperzine A (HupA) have been in use for centuries.

Zymenta provides a standardized amount of HupA, a potent, reversible AChEI derived from the Chinese club moss *Huperzia serrata*, which is routinely prescribed as a medical treatment for AD in China. HupA has high bioavailability and easily crosses the blood-brain barrier (Wang et al. 457-65;Fu and Li). HupA is highly specific for the predominant acetylcholinesterase isoform in the human brain (Wollen 223-44) and has been shown in several clinical trials to improve cognitive function in AD (Wang et al. 457-65;Fu and Li). In addition, HupA, presumably through its ACh-supporting effects, has been shown to protect against the formation of β-amyloid plaques (Zhang, Yan, and Tang 173-83;Wang, Yan, and Tang 1-26;Fu and Li), prevent glutamate excitotoxicity (Wang, Yan, and Tang 1-26), and reduce inflammatory cytokines (Swardfager et al.) that are associated with progression from MCI to AD (Diniz et al.). Thus, HupA provides multidimensional benefits for nutritional management of this disease. HupA has minimal peripheral effects, and evidence suggests that it may be more effective and better tolerated than synthetic AChEIs (Wang et al. 649-64).

As mentioned, AChEIs are routinely prescribed to patients with MCI, and AChEIs are the most common medication for AD. Due to the HupA content, Zymenta is not recommended for people using AChEI medication. Cerelist does not contain Hup A in order to provide the needed nutritional support for patients with MCI or mild-to-moderate AD who are already using AChEI medications.

Choline – an ACh precursor in limited supply

While AChEI compounds have demonstrated efficacy in slowing the progression of AD, it is unclear whether these agents affect choline levels. If systemic choline is low, the body may meet certain metabolic demands by removing choline from neuronal cell membranes (Ulus et al. 217-27), upregulating acetylcholinesterase activity, or reducing activity of choline acetyltransferase, the enzyme that joins choline and acetyl-CoA to form ACh (Liapi et al. 269-76). All of these actions may result in reduced availability of choline for ACh synthesis, thereby

counteracting the potential benefits of AChEIs. Therefore, choline supplementation should be considered as an adjunct to AChEIs to ensure adequate choline availability for ACh synthesis.

Choline is an essential nutrient necessary for lipoprotein transport throughout the body, methylation reactions, maintenance of cellular membrane integrity, and normal liver and muscle function (Zeisel and da Costa 615-23). In the brain, choline is a component of phospholipids that are necessary for structure and function of healthy brain cells. Choline is also an essential precursor for the synthesis of ACh, the central cholinergic neurotransmitter necessary for various dimensions of cognitive function, including learning, recalling, computing, and performing routine activities.

Adequate dietary choline intake is essential for health as low choline availability has been shown to lead to liver and muscle dysfunction, heart disease, and inflammation (Zeisel). Low choline is also associated with neurological impairments, including impaired cognitive performance (Kochunov et al. 1190-99), MCI, and AD (Kantarci et al. 1330-39;Watanabe, Shiino, and Akiguchi 71-77). Non-modifiable factors including age, gender, and genetics influence the risk for developing choline deficiency symptoms. Premenopausal women tend to be at lower risk for choline deficiency compared to men and post-menopausal women due to a protective effect of estrogen on choline status (Resseguie et al. 2622-32). However, as much as 50% of the population carry single nucleotide polymorphisms that markedly increase the risk of choline deficiency, regardless of estrogen status (Kohlmeier et al. 16025-30;da Costa et al. 1336-44;Ivanov et al. 313-18;Niculescu and Zeisel 2333S-5S;Zeisel). Choline requirements and risk of deficiency can also increase when intake or absorption of certain B-vitamins, such as folate or vitamin B12, is low (Jacob et al. 712-17;Niculescu and Zeisel 2333S-5S;Ivanov et al. 313-18;Kohlmeier et al. 16025-30), which is not uncommon among aging populations (Werder 159-95). Moreover, choline deficiency symptoms may be precipitated when illness or hospitalization results in limited food intake. Despite these findings, little attention has been given to the importance of achieving adequate choline intake for maintaining neurological and overall health (Zeisel and da Costa 615-23).

Human endogenous production of choline is insufficient to meet metabolic demands, and therefore we rely chiefly on dietary intake for the majority of our choline. However, most American diets contain few concentrated food sources of choline, with the exception of eggs. In addition, choline is not commonly used in food fortification or in multivitamin preparations typically intended to bridge nutrient gaps. Thus, achieving sufficient choline intake through food consumption can be challenging for individuals, particularly those following diets that limit calories, fat, cholesterol, or animal products, or for those avoiding certain allergenic foods.

Studies have shown that many individuals require choline intake at amounts well above current recommendations in order to reverse deficiency symptoms (Sha et al. 2962-75;Fischer et al. 1275-85). This has led to a recent proposal that the recommended Adequate Intake for choline be increased (Zeisel and da Costa 615-23). Yet, with approximately 90% of American adults already failing to meet the Adequate Intake (Zeisel and da Costa 615-23;Bidulescu et al. 14;Sha et al. 2962-75;Fischer et al. 1275-85), recommendations to increase choline intake will have little effect unless awareness and dietary distribution improve.

Choline intake in adults is inversely related to age, with individuals over age 70 averaging less than half of the recommended Adequate Intake per day (Zeisel and da Costa 615-23). Given the risk factors for choline deficiency and the challenges to meet demands from dietary sources, choline supplementation to support ACh synthesis is indicated for patients with cholinergic impairments such as those reported in MCI and the early stages of AD. While not all studies support the benefits of choline supplementation for cognitive performance (Kidd 85-115), studies showing increased brain choline concentration (Babb et al. 248-54;Babb et al. 1-9), preservation of cell membrane structure (Zhao, Frohman, and Blusztajn 16), and stimulation of ACh production (Ulus et al. 217-27) in response to exogenous choline support the contention that choline is essential for healthy neurological function (Parnetti et al. 159-64).

Zymenta and Cerelist each include two forms of choline to support the body's choline needs. Choline bitartrate helps ensure overall adequate choline supply, so total body demands can be met without drawing from the central nervous system supply. Alpha-glycerylphosphorylcholine (α-GPC) provides choline in a form that readily crosses the blood-brain barrier to meet central cholinergic demands. In addition, Zymenta and Cerelist contain acetyl-L-carnitine, which provides an acetyl group for the formation of ACh in the brain. In the central nervous system, the enzyme choline acetyltransferase facilitates the synthesis of ACh from acetyl-L-carnitine and α-GPC (Nalecz and Nalecz 597-609). These medical foods also contains folate, vitamin B12, and vitamin B6, which have all been found to modulate choline metabolism.

Nutrients to protect brain cell structure and function

The brain is a region of high metabolic activity that yields free radicals which, with advanced age, exceed the brain's antioxidant capacity. The resultant oxidative damage, in combination with sustained presence of inflammation, promotes the continuation of cellular damage and symptom progression in AD patients. Therefore, an additional means by which Zymenta and Cerelist support cholinergic activity and overall brain health is by providing ingredients that help conserve the structural integrity and promote healthy metabolic functions of brain cells.

For example, HupA, found in Zymenta, has been shown to increase neuronal growth factor which stimulates generation of new neurons (Zhang, Yan, and Tang 173-83;Wang, Yan, and Tang 1-26). Choline is not only a precursor for ACh, but also a structural and functional component of cellular membranes, helping to maintain integrity of brain cells. In addition, choline and the B vitamins are involved in DNA methylation pathways and, as such, support cellular function and replication (Coppede 246-60;Mason 941S-7S). Choline and B vitamins can also lower elevated homocysteine, a risk factor for AD (Werder 159-95). In addition to its role as an acetyl donor for ACh synthesis, acetyl-L-carnitine is an intermediate necessary for cellular energy metabolism.

Zymenta and Cerelist also contain α-lipoic acid which, like α-GPC and acetyl-L-carnitine, readily crosses the blood-brain barrier. Once in the brain, it supports brain cell metabolism by enhancing insulin sensitivity and promoting brain glucose uptake, which is commonly impaired in AD (Maczurek et al. 1463-70). Lipoic acid has also been shown to activate choline acetyltransferase activity to promote ACh synthesis (Maczurek et al. 1463-70). In addition, α-lipoic acid provides neuroprotective effects (Goraca and slanowicz-Antkowiak 141-46;Saeed et al. e2459), prevents deleterious age-associated changes in brain cell gene expression (Park et al. 484-95), and acts synergistically with acetyl-L-carnitine to scavenge free radicals for neuronal protection (Aliev et al. 320-33;Hagen et al. 1870-75;Liu et al. 2356-61;Long et al. 755-63;Shenk et al. 199-206;Abdul and Butterfield 371-84) and the enhancement of cognitive performance (Milgram et al. 3756-62;Liu et al. 2356-61;Shenk et al. 199-206).

SUMMARY

Mild cognitive impairment and Alzheimer's disease are complex and progressive diseases with ultimately devastating effects and no known cure. Use of AChEIs to support cholinergic function and brain health early in the disease process or following diagnosis can help slow the progression of symptoms and maintain quality of life for patients and their caregivers. However, widespread nutritional deficits may hinder the therapeutic potential of existing pharmaceutical compounds. To address this medical need, Zymenta and Cerelist have been formulated to nutritionally manage cholinergic activity through a unique and complementary multi-pronged approach that provides: 1) ACh precursors to support its synthesis; 2) a natural potent AChEI to prolong ACh half-life (Zymenta only); and 3) protective nutrients to support brain cell integrity and function. By addressing under-recognized, highly prevalent nutritional deficits in combination with well-established traditional interventions, Zymenta and Cerelist may offer a beneficial therapeutic edge to patients with MCI and mild-to-moderate AD.

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