Interaction of ω-3 fatty acids with B vitamins in slowing the progression of brain atrophy: identifying the elderly at risk

Imrich Blasko*

Memory Clinic, Division of General and Social Psychiatry, Department of Psychiatry and Psychotherapy, Innsbruck Medical University, Innsbruck, Austria

Identifying elderly persons with a higher risk of the development of dementia represents a challenge for clinicians and public health authorities. Early detection of cognitive disturbances has guided the conceptualization of mild cognitive impairment (MCI). The potential advantage of this approach lies in the identification of predementia stages and distinguishing them from normal aging. Combining parameters such as the preservation of independence in functional abilities of daily life with positive biomarkers also offers the possibility of diagnosing MCI preceding Alzheimer disease (1). Although not yet applicable for everyday clinical use, this is a significant step forward.

Ideally, clinical classification should lead to the development of new medications. Disappointingly, over the past decade no new medications for Alzheimer disease dementia or for its preclinical stages have been approved. Negative trials of interventions aiming at Alzheimer dementia have therefore raised discussions about current disease-modifying strategies (2). Agreement arose, however, that hitting the right biological targets at the appropriate disease stages will be essential. One such target could be addressing enhanced homocysteine concentrations in persons with a clinical diagnosis of MCI.

Homocysteine is a metabolic product of amino acid methionine and is a key intermediate in pathophysiologic processes associated with oxidative stress. Thus, homocysteine, fatty acids, and the enzymes involved in their metabolism may play an integrating role in translating the effects of oxidative stress independently of the initial pathophysiologic source. Following these considerations, homocysteine could represent an unspecific marker that represents a downstream risk variable of many illnesses of vascular and neurodegenerative origin.

In this issue of the Journal, Jernerén et al. (3) report remarkable data from the randomized, placebo-controlled VITACOG (Homocysteine and B Vitamins in Cognitive Impairment) trial. This study was designed to see if lowering total homocysteine concentrations by the administration of high doses of supplementary B vitamins (folic acid and vitamins B-6 and B-12) over 2 y would slow down the rate of brain atrophy in elderly subjects with MCI. Brain atrophy served as a proxy variable of neuronal injury. Consequently, slowing the rate of brain atrophy should be accompanied by a reduction in cognitive deterioration. Previous reports from this trial found that treatment response to B vitamins is related to baseline homocysteine concentrations. The atrophy rate in participants with high baseline homocysteine concentrations was halved in the active treatment group, and this effect was associated with a slowing of cognitive and clinical decline (4, 5). In the present study, the authors examined whether the plasma concentrations of omega-3 (ω-3) fatty acids (EPA + DHA) modify the treatment effect of homocysteine-lowering B vitamins. The study included 168 elderly subjects (aged ≥70 y) assigned to receive either placebo or daily high-dose B vitamins for 24 mo. Covarying for baseline ω-3 fatty acid concentrations showed a significant interaction between treatment response and plasma ω-3 fatty acids with regard to brain atrophy rates. B vitamins slowed the atrophy rate by 40.0% in the high baseline ω-3 fatty acids (≥590 μmol/L) group compared with placebo. B vitamins had no effect on atrophy among subjects with low baseline ω-3 fatty acid concentrations (<390 μmol/L). The authors concluded that the effect of B vitamins on brain atrophy progression depends on pre-existing plasma ω-3 fatty acid concentrations.

Even when considering limitations such as small group size and the need for replication, this observation has important implications. First, the findings tighten the link between ω-3 fatty acids and B-vitamin metabolism. The mechanism by which ω-3 fatty acids are thought to exert their protective effect is by stimulating neurite outgrowth and reducing reactive oxygen species production (6). It appears that a sufficient B-vitamin status and low homocysteine concentrations are required for an optimal utilization and distribution of ω-3 fatty acids. Humans should ingest ω-3 fatty acids, B vitamins, or folic acid through diet, mainly from fish, nuts, and vegetables, which are often lacking in the typical Western diet. DHA is highly enriched in brain phospholipids and must be imported across the blood-brain barrier (BBB). Recently, a protein candidate was identified for DHA transport via the BBB (7). Various oxidant mechanisms can impair the function of DHA. New insights should lead to the development of new medications for Alzheimer disease dementia or for its preclinical stages. Even when considering limitations such as small group size and the need for replication, this observation has important implications. First, the findings tighten the link between ω-3 fatty acids and B-vitamin metabolism. The mechanism by which ω-3 fatty acids are thought to exert their protective effect is by stimulating neurite outgrowth and reducing reactive oxygen species production (6). It appears that a sufficient B-vitamin status and low homocysteine concentrations are required for an optimal utilization and distribution of ω-3 fatty acids. Humans should ingest ω-3 fatty acids, B vitamins, or folic acid through diet, mainly from fish, nuts, and vegetables, which are often lacking in the typical Western diet. DHA is highly enriched in brain phospholipids and must be imported across the blood-brain barrier (BBB). Recently, a protein candidate was identified for DHA transport via the BBB (7). Various oxidant mechanisms can impair the function of DHA. New insights should lead to the development of new medications for Alzheimer disease dementia or for its preclinical stages.

*To whom correspondence should be addressed. E-mail: imrich.blasko@i-med.ac.at.

1 Abbreviations used: BBB, blood-brain barrier; MCI, mild cognitive impairment; VITACOG, Homocysteine and B Vitamins in Cognitive Impairment.
of the BBB and thereby increase the vulnerability of the neurovascular unit.

Second, these data may improve our understanding in identifying elderly persons who could benefit from supplementation with B vitamins and/or ω-3 fatty acids. In this context, it is important to note that the annual conversion rate from MCI to dementia varies between 5% and 10% and most people with MCI will not progress to dementia even after 10 y of follow-up (8). We still do not know whether higher homocysteine concentrations predict conversion. The double-blind period of the VITACOG trial (5) ended ~5 y ago and a report on the conversion rates to dementia in this population is eagerly awaited.

A recent meta-analysis found homocysteine-lowering B vitamins to have no significant effect on global cognitive function (9). This meta-analysis should be interpreted by taking the considerable heterogeneity of included studies into account. Including cognitively healthy and impaired persons at different disease stages presents a significant problem. Stratifying by clinical risk stages, including biomarkers such as amyloid-β and τ proteins, would seem prudent when evaluating a potential effect of such intervention, especially also with respect to evidence that the risk conferred by the apolipoprotein E gene (ε4 allele) could be attenuated by supplementation with DHA (10).

How should we select persons for future nutrient-based therapeutic interventions? It seems conceivable that they will need to fulfill criteria for MCI. Whether homocysteine concentrations should figure into the selection criteria, however, remains to be determined. The present work of Jernerén et al. certainly suggests that ω-3 fatty acid plasma concentrations play an important role in the prestudy workup.

In principle, this study is also a good example of a well-designed nutritional intervention. Although individualized risk screening is well accepted in the field of medicine, there are clearly many open questions before this model could become applicable for the cognitively impaired elderly. This highlights the need for further controlled studies clarifying the potential of B vitamins and ω-3 fatty acids in persons at an increased risk of developing dementia.

I thank Wolfgang W Fleischhacker for editing assistance. The author has received speaker honoraria from Wörwag Pharma GmbH, Germany. There were no other conflicts of interest.

REFERENCES