CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO DEMENTIA: INFLUENCE OF FOLIC ACID AND VITAMIN B12 USE IN THE VITA COHORT

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Abstract: Objective: Increased serum homocysteine and low folate levels are associated with a higher rate of conversion to dementia. This study examined the influence of vitamin B12/folic acid intake on the conversion from mild cognitive impairment (MCI) to dementia. Participants: A community dwelling cohort of older adults (N=81) from the Vienna Transdanube aging study with MCI. Design: Prospective study with a retrospective evaluation of vitamin intake. Measurements: Laboratory measurements, brain magnetic resonance imaging, and cognitive functioning were assessed at baseline and at five-year follow-up. Results: The self-reported combined use of folic acid and vitamin B12 for more than one year was associated with a lower conversion rate to dementia. Serum levels of homocysteine and vitamin B12 as measured at baseline or at five years were not associated with conversion. Higher folate levels at baseline in females predicted a lower conversion rate to dementia. The assessment of brain morphological parameters by magnetic resonance imaging revealed higher serum folate at baseline, predicting lower medial temporal lobe atrophy and higher levels of homocysteine at baseline, predicting moderate/severe global brain atrophy at five years. Users of vitamin B12 or folate, independent of time and pattern of use, had lower grades of periventricular hyperintensities and lower grades of deep white matter lesions as compared to non-users. Conclusions: These results from a middle European study support observations on the protective ability of folate in MCI patients with respect to conversion to dementia; they also point to a participation of homocysteine metabolism on processes associated with brain atrophy.

Key words: Folic acid, vitamin B12, homocysteine, mild cognitive impairment, dementia.

Introduction

Current therapy of age-associated dementia includes the use of acetylcholine esterase inhibitors and N-methyl-d-aspartate (NMDA) receptor antagonists memantine. In the past decade no further substances were added for clinical use, although a number of treatment strategies were tested in clinical studies. New treatment options and improved selection criteria of patients are needed. For these reasons, well known substances which influence important steps in neurodegeneration, such as oxidative stress and inflammation, have been tested for their efficacy.

The aging brain shows a slow progressive atrophy which can be accelerated by the conversion from mild cognitive impairment (MCI) to dementia. Several efforts were made to identify possible contributing factors to this decline. A higher serum level of total homocysteine was shown to be one of the contributing factors. Homocysteine, a sulfur-containing amino acid derived from methionine, is a risk factor for developing vascular disease, brain atrophy, cognitive impairment and Alzheimer’s Disease (AD) (1). In the elderly, cognitive impairment and incident dementia may be related to the high prevalence of an inadequate B vitamin status and an elevation in plasma homocysteine levels (2, 3).

As many as 77 cross-sectional studies on more than 34,000 subjects, as well as 33 prospective studies on more than 12,000 subjects, have shown associations between cognitive deficit or dementia and homocysteine and/or B vitamin status (4-6). These studies suggest that elevated concentrations of total homocysteine and/or low-normal concentrations of B vitamins (folate, vitamin B6, and vitamin B12) are associated with an increased risk of brain atrophy and the development of cognitive impairment and dementia in the elderly (7).

Surprisingly, a recent Cochrane Database Review has concluded that there is no consistent evidence that folate, with or without vitamin B12, has a beneficial effect on cognitive function of unselected healthy or cognitively impaired older people (8).

In a randomized, double-blind controlled trial of homocysteine-lowering B vitamins, MCI patients using B vitamins showed slowing of the accelerated rate of brain atrophy (9). The treatment response was related to baseline homocysteine levels, with more severe atrophy occurring in persons with higher homocysteine levels. Recently, the same trial (VITACOG) has reported positive cognitive outcomes in which, B vitamins appear to slow cognitive and clinical decline in people with MCI, in particular in those with elevated homocysteine (10).

We analyzed a sub-group of the middle European cohort of the Vienna Transdanube Aging Study (VITA). These individuals were already showing mild cognitive impairment at baseline. The aim of our study was to determine whether the
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Methods

Study population, recruitment and rate of conversion

These analyses originate from the Vienna Transdanube Aging Study (VITA), a population-based study of 75 year-old residents of Vienna, Austria. The recruiting procedures are described in detail elsewhere (12). Briefly, VITA began in 2000-2002 with a baseline examination of 606 persons (40 % of 1505 contacted) born between May 1925 and April 1926. Participants were re-examined every 2.5 years from baseline. Data from the baseline and five-year follow-up is included in the following analyses. The study was approved by the local Ethics Committee of the Vienna Medical University. Subjects were informed about the specific procedures and gave their written informed consent.

All 141 persons with mild cognitive impairment (MCI) at baseline from the VITA cohort were included in this study. At five-year follow-up, 83 persons were re-investigated. As presented in the flow chart (Fig. 1), 29 probands declined to participate. The reasons for this included lack of interest, somatic morbidity, obvious affective difficulties, and lack of time. Two persons underwent a partial investigation (telephone interview) without blood sampling (13). 20 individuals (25%) participated in face-to-face interviews by experienced specialist raters, lasting approximately 9 hours per subject. Medical history was obtained from the tested subjects, their medical documentation and, if necessary, from relatives. The serum samples collected for homocysteine, folate, and vitamin B12 were drawn following overnight fasting. Neuropsychological testing and an MRI were performed on the same day.

The information on folic acid and vitamin B12 supplementation was obtained from study participants during a clinical interview. The participants were asked to bring all medication to the appointment. In those persons who supplemented vitamins, the mean daily dose of folic acid was 1.8±2.1 mg/day (±SD), range 0.1-5 mg and in case of vitamin B12 it was 146.3±258.8 μg/day, range 1-1000 μg. Corroborating information on drug exposure was obtained through medical records, as well as through information of caregivers or relatives. When a subject was determined to have not previously consumed folic acid and vitamin B12, yet their serum levels were markedly increased (folate >20 ng/ml; vitamin B12 > 1200 pg/ml), they were categorised as having consumed folic acid and vitamin B12 for a period of one month only.

Figure 1

Flow chart of studied population, which represents selected persons with mild cognitive impairment at baseline. For classifications see Methods; AD - Alzheimer’s disease, FTLD - Frontotemporal lobe dementia, DLB - Dementia with Lewy bodies

51 of 81 individuals with MCI at baseline did not report the use of either folic acid or vitamin B12 during the observation period of five years. 10 individuals who had used a combination of folic acid and vitamin B12 for more than one year were assigned to the group of “combination users”. 14 individuals who used either folic acid or vitamin B12 for more than one year, 4 individuals who used either folic acid or vitamin B12 for less than one year, and 2 individuals who used a combination of both for a period of less than one year were assigned to the group of “inconsistent users”.

Of 49 individuals with dementia, 2 (4.1%) belonged to the group of “combination users”, 15 (30.6%) were “inconsistent users” and 32 (65.3%) had not consumed folic acid and/or vitamin B12 in the past five years. In the MCI/cognitively unimpaired group, 8 persons (25%) belonged to the group of “combination users”, 5 persons (15.6%) were “inconsistent users” and 19 persons (59.4%) had not used either substance.

Variables used in this study include serum levels of homocysteine, folate, vitamin B12, creatinine, years of education, as well as the presence of at least one APOE ε4 allele.