

Plasma betacarotene in Alzheimer's disease. Association with cerebrospinal fluid beta-amyloid 1-40, (Abeta40), beta-amyloid 1-42 (Abeta42) and total Tau

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Abstract

We studied the plasma betacarotene concentrations in 40 Alzheimer's disease patients and the association with cerebrospinal fluid beta-amyloid 1-40, (Abeta40), cerebrospinal fluid beta-amyloid 1-42 (Abeta42) and cerebrospinal fluid total Tau. We found that patients with plasma beta carotene levels below the 25th percentile had 55% reduced ratios of Abeta40/Tau and 51% reduced ratios of Abeta 40/Abeta 42 compared with patients in the highest quartile. Mean Tau concentrations in the lowest quartile of plasma beta-carotene levels were 74% higher compared with the highest quartile of plasma beta-carotene levels. Thus, we could demonstrate an statistically significant association between beta carotene levels in plasma and neurochemical markers in the cerebrospinal fluid of Alzheimer's disease patients.

Introduction

Beta-Carotene and vitamine A (Retinol, Retinal, Retinoic acid) show potent anti-amyloidogenic and fibril-destabilizing effects in vitro (Ono et al. 2003, Ono et al. 2004). They also inhibit the generation and growth of beta-amyloid fibrils (fAbeta) in a dose dependent way. Additionally, Vitamine A and Beta-Carotene destabilize preformed fAbeta in a dose dependent way (Ono et al. 2003, Ono et al. 2004). Based on these findings, it was hypothesized that vitamine A and Beta-carotene could be possible agents for the prevention and therapy of Alzheimer's disease. Many studies have shown a correlation of the CSF concentrations of Abeta40, Abeta42 and total Tau with the diagnosis and progression of Alzheimer's disease. Today, the

neurochemical diagnosis of Morbus Alzheimer is based on the CSF concentrations of Abeta42, total Tau, the ratio of Abeta42 to Abeta40 and the ratio of Abeta42 to total Tau (Lewczuk et al. 2004).

In this study we investigated the possible association between plasma beta-carotene levels and cerebrospinal fluid concentrations of Abeta40, Abeta42, total Tau and their ratios.

Materials, methods and patients

Patients were diagnosed according to the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders

Association) criteria (Ganzer et al. 2003, Stuerenburg et al. 2005, Stuerenburg et al. 2004, Stuerenburg et al. 2004). Clinical evaluation included detailed medical history, psychiatric, somatic and neurological status, neuropsychological testing, routine blood tests, an electroencephalogram, a computed tomography scan or magnetic resonance imaging. The Mini-Mental-Status examination (MMSE) test was used for staging severity of cognitive impairment and was performed prior to the start of any treatment affecting the central nervous system (e.g. acetylcholine esterase inhibitors, antidepressants or antipsychotic drugs).

Results

We examined 40 patients. 27 patients were female, 13 were male. The mean age was $71,6 \pm 1,6$ years (mean \pm standard error). All patients had a diagnosis of Alzheimer's disease, the mean MMSE score was $16,2 \pm 1,2$. Mean concentration of plasma Beta-carotene was $0,63 \pm 0,12 \mu\text{Mol/l}$.

According to their plasma concentration of beta-carotene, patients were grouped into four quartiles (i.e. the lowest quartile included those patients with plasma values below the 25th percentile; the highest quartile included patients with plasma concentrations above the 75th percentile).

We used multivariate analysis of variance (MANOVA) to examine differences between these groups with regard to cerebrospinal fluid (csf) concentrations of total Tau, abeta40, abeta42, and clinical parameters such as MMSE.

CSF total Tau was significantly higher in the 2nd quartile of plasma beta-carotene compared to the 3rd and 4th quartile ($p < 0.05$). Mean values of total Tau were $312,2 \pm 83,7 \mu\text{Mol/l}$ in the highest quartile of plasma beta-carotene ($n=8$), $354,1 \pm 79,2$ in the 3rd quartile ($n=7$), $705,8 \pm 121,7$ in the 2nd quartile ($n=14$), and $543,3 \pm 93,4$ in the lowest quartile ($n=11$). Therefore the CSF total tau concentration in the lowest quartile of plasma beta-carotene was elevated by 74% compared with the highest quartile of beta-carotene.

Also, CSF concentrations of abeta40 were significantly lower in the lowest quartile of plasma beta-carotene compared with all other quartiles ($p < 0.05$). Mean abeta concentrations were $7,9 \pm 0,8 \text{ ng/ml}$ in the highest quartile, $7,6 \pm 1,0 \text{ ng/ml}$ in the 3rd quartile, $7,4 \pm 1,0 \text{ ng/ml}$ in the 2nd quartile, and $4,7 \pm 0,89 \text{ ng/ml}$ in the 1st quartile. CSF abeta40 in the 1st quartile of plasma beta-carotene was elevated by 59,5% compared with the 4th quartile. There were no significant differences between quartiles with regard to CSF abeta42. Mean concentrations of CSF Abeta 42 were $0,21 \pm 0,03 \text{ ng/ml}$ in the highest quartile, $0,16 \pm 0,01 \text{ ng/ml}$ in the 3rd quartile, $0,22 \pm 0,02 \text{ ng/ml}$ in the 2nd quartile, and $0,24 \pm 0,03 \text{ ng/ml}$ in the 1st quartile. Ratios of CSF Abeta40:Abeta42 were significantly lower in the lowest quartile of plasma beta-carotene compared with the 3rd and 4th quartile ($p < 0.05$). Mean ratios of CSF Abeta40:Abeta42 were $45,1 \pm 7,3$ in the 4th quartile, $50,7 \pm 9,0$ in the 3rd quartile, $39,3 \pm 8,1$ in the 2nd quartile, and $22,0 \pm 4,5$ in the 1st

quartile. There were no significant differences between quartiles concerning the ratio of CSF Abeta42:Tau. Ratios of CSF Abeta40:Tau were significantly different between the 1st and 2nd quartile compared with the 4th quartile of plasma beta-carotene ($p < 0.05$). The ratio of Abeta40/total Tau in the 1st quartile of plasma beta-carotene was decreased by 55%, in the second quartile by 51% compared to the highest quartile.

There were no differences between quartiles of plasma beta-carotene with regard to the frequency of apolipoprotein Epsilon 4 allele ($P = 0,77$), education measured by highest degree ($p = 0,35$), and occupational level ($P = 0,53$). Also, there were no differences concerning sex ($P = 0,96$) or age ($P = 0,83$) of the patients in the different quartiles. MMSE-values did not differ between quartiles: highest quartile $15,5 \pm 2,8$, 3rd quartile $16,1 \pm 3,6$, 2nd quartile $17,3 \pm 1,8$, and 1st quartile $15,4 \pm 2,2$.

Discussion

To our knowledge, this is the first study in patients with Alzheimer's disease demonstrating an association between plasma beta-carotene levels and CSF concentrations of Abeta40, Abeta42, total Tau and their ratios. Patients with plasma beta carotene levels below the 25th percentile had 55% reduced ratios of Abeta40/Tau and 51% reduced ratios of Abeta 40/Abeta 42 compared with patients in the highest quartile. Mean Tau concentrations in the lowest quartile of plasma beta-carotene were 74% higher compared with the highest quartile. Thus, we demonstrated an association between beta carotene levels in plasma with neurochemical markers of Alzheimer's disease in the CSF.

There was no evidence of an association between education, sex, age or APOE status and plasma beta carotene levels. Our results are consistent with in vitro studies of a potential anti-amyloid effect of beta carotene. However, it is currently unclear if plasma beta carotene itself has a direct effect or serves rather as surrogate marker of a healthy diet with fruits and vegetables that include beta carotene and might have a protective effect on the development of Alzheimer's disease. It can be speculated that a beta carotene-rich diet might have protective effects with regard to the development and course of Alzheimer's disease and minimal cognitive impairment.

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