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The influence of smoking on plasma folate and lipoproteins in Alzheimer disease, mild cognitive impairment and depression

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Abstract

The risk for Alzheimer's disease (AD) is associated with lifestyle factors, especially cigarette smoking. In this study we investigated the influence of smoking on the serum levels of folic acid, LDL and HDL in AD patients, patients with minimal cognitive impairment (MCI) and patients with major depression. We investigated a total of n = 374 patients in the diagnostic categories:, AD: n = 272, MCI: n = 60, Major depression: n = 42. We found significantly lower HDL levels in smokers and previous smokers in comparison to non-smokers, p<0,05. The LDL: HDL ratio in smokers was significant higher (+20%) compared to previous smokers and non-smokers, p < 0.05. The mean levels of folic acid were statistically significant (p<0.05) lower (–24%) in smokers compared to non-smokers.

Patients with MCI and Alzheimer`s disease (and also major depression) who are "smokers" show serum levels of HDL and folic acid that are known to be strong risk factors for vascular damage and increased risk for vascular brain damage and impaired cognitive function. Therefore cessation of smoking, substitution with folate or statin therapy of smoking patients with MCI or AD might be beneficial to slow down further cognitive decline.

Introduction

Recent studies showed that the risk for Alzheimer's disease (AD) is associated with lifestyle factors, especially cigarette smoking. Smokers have a 2.72 higher risk for Alzheimer's disease and a 1.98 higher risk for vascular dementia than non-smokers. Heavy smokers even showed 3.0 higher risk for Alzheimer's disease (Joan et. al 2004). Recent studies are discussing whether the association between the deficiency of folic acid and AD is based on elevated homocysteine or on direct mechanisms (Bunce, et. al, 2004; Miller et. al, 2003, Morris, 2003; Miller et al, 2002; Serot et al. 2001, Snowdon et. al, 2000; Nourhashemi et. al, 2000). A study with catholic nuns showed a corre-

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lation between concentrations of folic acid and brain atrophy in a subgroup of 15 nuns that had a sicnificant number of AD lesions in their neocortices (R= 0,8, P = 0,0006). The authors hypothesized that the brain atrophy was due to low concentrations of folic acid because no other of the investigated nutrition factors showed a correlation with the atrophy (Snowdon et al. 2000). To reach sufficiently low serum homocysteine levels one would need to double the generally accepted norm values for folic acid (Lewis et. al, 1992). In this study we investigated the influence of the lifestyle factor smoking on the serum levels of folic acid, LDL and HDL in AD patients, patients with minimal cognitive impairment (MCI) and patients with major depression.

Material, 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. 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). Depression: For assessing depression the following scales were used: The 15-point Geriatric Depression Scale (GDS), a short form of a 30-point scale which is a self-rating scale that is widely established in geriatric settings. We investigated a total of 374 patients which could be divided into the following diagnostic categories:, AD: N = 272, MCI: N = 60, Major depression: N = 42.

Results

Overall, 205 female and 169 male patients were investigated. Significant differences in gender between the diagnostic groups were not found. The mean age was 70,1 years ± 0,5. The mean age of AD patients was 71,5 ± 0,5 years, of MCI patients 67,9 ± 1,44 years and of major depression patients 64,2 ± 1,55 years. There was no significant difference of serum HDL levels between the different diagnosic groups. The mean HDL was 53,2 ± 0,99 mg/dl in AD, 52,2 ± 2,2 mg/dl in MCI and 51,9 ± 2,85 mg/dl in major depression. The mean serum levels of LDL were significantly higher in AD patients (140,3 ± 2,1 mg/dl) in comparison to MCI patients (130,6 ± 4,2 mg/dl) and patients with major depression (129,2 ± 5,46 mg/dl, p<0,05). However, there was no significant difference in the medication with statins between the diagnostic groups, p>0.05. There was no significant difference in serum levels of folic acid between the diagnostic groups (AD: 6,8 ± 0,26 ng/ml, MCI: 7,96 ± 0,6 ng/ml, major depression 7,65 ± 0,7 ng/ml. To investigate the influence of smoking on the serum levels of folic acid, HDL and LDL we divided all patients into the following three groups: non-smokers (never smoked), n=212, previous smokers, n=115 and smokers (still smoking), n=47. We found significantly lower HDL levels in smokers (45,1 ± 2,55 mg/dl) and previous smokers in comparison to non-smokers, p<0,05. We also found significantly lower LDL levels in smokers (130,4 ± 5,8 mg/dl) and previous smokers (135,0 ± 2,9 mg/dl) in comparison to non-smokers (142,8 ± 2,6 mg/dl), p<0,05). The LDL:HDL ratio in smokers was 3,24 ± 0,23, 2,9 ± 0,1 in previous smokers and 2,73 ± 0,07 in non-smokers. The difference between non-smokers and smokers was statistically significant, p< 0,05. The LDL:HDL – ratio was 20% higher in smokers compared to non-smokers. There was no significant difference in the medication with statins between the groups, p>0.05. The mean levels of folic acid were 5,64 ± 0,47 ng/ml in smokers, 7,14 ± 0,42 ng/ml in previous smokers and 7,43 ± 0,32 mg/ml in non-smokers. The difference between smokers and non-smokers was statistically significant, p<0,05. The levels of folic acid were 24% lower in smokers in comparison to non-smokers.

Conclusions

In this study we found low serum levels of folic acid in a high percentage of patients with AD, MCI and major depression. We found significant lower levels of folic acid in „smokers", which in general suggests an important role of smoking on serum folic acid and especially in patients with dementia. Within the smokers subgroup, we further found a constellation of lipoproteins that is a strong risk factor for arteriosclerosis: low serum HDL levels and a high LDL: HDL ratio. Taken these findings together smokers and previous smokers show serum levels of lipoproteins and folic acid that are known to be strong risk factors for vascular damage and therefore increased risk for vascular brain damage and impaired cognitive function.

Therefore cessation of smoking, substitution with folate or statin therapy of smoking patients with MCI or AD might be beneficial to slow down further cognitive decline. Beneficial effects of folic acid substitution on non cognitive symptoms have been described before (Meins et al. 2000). The cost of this therapy would be low and there are no side effects described within this dose range. We could show, that in demented patients the lifestyle habit "smoking" might increase the risk of further vascular and neuronal damage by altering the serum levels of plasma lipoproteins and lowering the serum levels of plasma folic acid.

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