



The influence of vascular risk factors on cognitive decline in patients with Alzheimer's Disease



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ARTICLE INFO

Article history:

Received 12 February 2014

Received in revised form 1 June 2014

Accepted 23 June 2014

Keywords:

Alzheimer's Disease
Hypertension
Hypercholesterolemia
Diabetes mellitus
Overweight
Smoking.

ABSTRACT

Introduction: The influence of vascular risk factors (VRFs) on the rate of cognitive decline in patients with established dementia is unclear. This study aims to examine the association between VRFs and the rate of cognitive decline in patients with Alzheimer's disease (AD).

Methods: Data were obtained from patients visiting a memory clinic between 2004 and 2012. VRFs were determined at baseline and included hypertension, hypercholesterolemia, diabetes mellitus, overweight and smoking. Continuous values of blood pressure, total cholesterol, glucose level and body mass index were also obtained. Mini-Mental State Exam (MMSE) scores were obtained at baseline and during follow-up visits. The association between VRFs and the annual change in MMSE scores was analysed with a multivariable linear mixed model adjusted for age, sex and the aforementioned VRFs.

Results: From 174 patients (mean age 78.3 years), with a follow-up time up to 5.8 years (mean 1.1 year), in total 447 MMSE scores were obtained. The multivariable analyses showed an association between age as well as systolic blood pressure and a decline in annual rates of change in MMSE scores of -0.05 (95% confidence interval (CI): -0.09 to 0.00) and -0.01 (CI: -0.03 to 0.00), respectively. For all other VRFs, including sex, patients did not show a significant difference.

Conclusion: This study did not find an association between preventable vascular risk factors and cognitive decline in patients with AD, except for systolic blood pressure. As the association between systolic blood pressure and decline in MMSE was small, clinical relevance may be limited.

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1. Introduction

Dementia imposes a huge burden on society worldwide; an estimated 35.6 million people have been diagnosed with dementia and this number is expected to triple to 115.4 million people with dementia by 2050 due to ageing of the population. About 70% of these patients (80.7 million) will have Alzheimer's disease (AD) [1]. Vascular risk factors (VRFs) including hypertension (HT), hypercholesterolemia (HC), diabetes mellitus (DM), overweight and smoking are known to increase the risk of developing dementia [2]. As most VRFs are modifiable by lifestyle interventions and/or medical treatment, it is of clinical importance to understand the influence of these VRFs on cognitive decline. A recent review on the association of VRFs and cognitive decline in patients with dementia suggested an association between LDL-cholesterol and the progression of dementia, while inconsistent results were found for other VRFs [3]. Apart from the inconclusive results, most of the reviewed

studies did not examine the simultaneous influence of multiple VRFs on cognitive decline [3]. Additional cohort studies and experimental studies examining multiple VRFs were recommended to better understand the causal contribution of VRFs on cognitive decline in dementia [3]. The aim of the current cohort study was to evaluate whether different uncontrollable and preventable VRFs as well as multiple VRFs influence the rate of cognitive decline in patients with AD.

2. Methods

2.1. Data collection

For this cohort study, data from medical records were obtained from consecutive new patients who visited the memory clinic of the University Medical Center of Utrecht (UMCU) between 2004 and 2011. Follow-up visits were included until 31st of December 2012. Baseline data retrieved included age, sex, Mini-Mental State Exam (MMSE) [4] score, length, weight, education, smoking status, medication use, glucose level, cholesterol level, blood pressure, medical history including history of cerebrovascular disease or

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coronary heart disease. When patients visited the memory clinic again for follow-up visits, the MMSE scores and date of visits were obtained.

Patients eligible for this study were diagnosed with AD after a cognitive diagnostic assessment at the memory clinic. This assessment was conducted by a multidisciplinary geriatric team according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria [5], either at baseline or at a follow-up visit when supplementary diagnostics were finished. Patients were included when they had at least one follow-up MMSE score available after being diagnosed with AD. The number of follow-up visits and time between those visits differed per patient. All patients received treatment with acetylcholinesterase inhibitors as part of usual care. Individuals who were not able to provide an answer to at least 28 of the 30 items of the MMSE (due to being illiterate, not fluent in Dutch, or other reasons) were excluded as their scores might not be representative for their cognitive status.

2.2. Vascular risk factors

The different VRFs that were obtained at baseline (including HT, HC, DM, overweight and smoking) were defined as follows. Patients were defined as having HT when this was reported in their medical history, were using antihypertensive drugs (beta-blockers, diuretics, ACE-inhibitors, calcium-antagonists and AT2-antagonists), or had a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg at baseline. HC was defined as having HC reported in the medical history, using drugs for HC (statins) or having a total cholesterol level of ≥ 6.5 mmol/l at baseline. DM was defined as having DM reported in the medical history, using either oral antidiabetic drugs (sulfonylureas, biguanides, glinides, alpha-glucosidase inhibitors, thiazolidinediones, DPP-4 inhibitors and GLP-1 analogues) or insulin or having a glucose level of ≥ 11.0 mmol/l at baseline. When blood pressure measurements, cholesterol levels and/or glucose levels were not available, VRF status was based on medical history and medication use. Overweight was defined as having a body mass index (BMI) of ≥ 25 kg/m², as calculated by weight(kg)/length²(m). Patients were defined as smokers when they currently smoked and defined as non-smokers when they had never smoked or had quit smoking.

2.3. Statistical analyses

The association between VRFs and annual rate of change in MMSE scores from baseline was studied using a repeated-measures multivariable linear mixed-effects model. Both the effects of single VRFs and of multiple VRFs (defined as having two or more VRFs and subsequently also as having three or more VRFs) were analysed. Single VRFs were analysed as continuous variables (systolic blood pressure, diastolic blood pressure, cholesterol, glucose and BMI) as well as dichotomous variables (HT, HC, DM, overweight and smoking). The repeated measurements were the time points of the MMSE measurements at baseline and follow-up visits. Fixed effects were age, sex, HT, HC, DM, overweight and smoking. Random effects within the model were intercept and slope for individual participants. Analyses were unadjusted, adjusted for age and sex, and then additionally adjusted for HT, HC, DM, overweight and smoking. The two-sided significance level of 5% and 95% confidence interval (CI) were used for statistical inference. Statistical analyses were performed using the R statistics program, version 2.15.2 (R Core Team, 2012. R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Overall, 936 new patients visited the memory clinic between 2004 and 2011. Of these, 180 were diagnosed with AD and had at

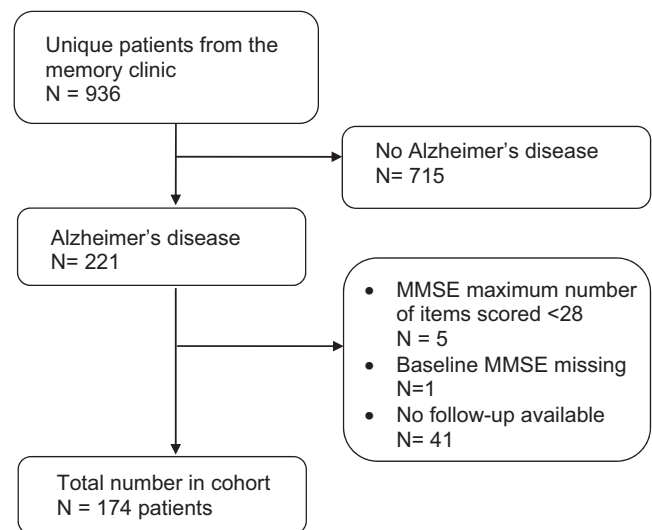


Fig. 1. Selection of the study population.

least one follow-up MMSE available. We excluded 6 patients; five patients did not meet the criteria for answering at least 28 items of the MMSE, and one patient's baseline MMSE score could not be retrieved due to unclear communication in the medical record. Thus, in total, this cohort consisted of 174 patients with AD from whom 447 MMSE scores were obtained during follow-up. The mean follow-up time was 1.1 (± 1.1) years with a maximum of 5.8 years. A flow diagram of the patient selection process is provided in Fig. 1.

Table 1 shows the baseline characteristics of the patients. Mean age was 78.3 years (SD 7.5) and 55.7% were female. Mean MMSE score was 21.4 ± 4.4 at baseline. HT was the most frequent VRF with a prevalence of 85.6%.

Table 2 shows the results of the univariable and multivariable analyses between annual change in MMSE and VRFs. Of all risk factors examined, age and systolic blood pressure were significantly associated with an increased deterioration of annual cognitive function. Patients with a higher age showed more annual cognitive decline compared to younger patients ($\beta = -0.05$ (95% CI -0.09 ; 0.00)) and patients with a higher systolic blood pressure had more decline compared to patients with lower blood pressures ($\beta = -0.01$ (-0.03 ; 0.00)).

All other VRFs (HC, total cholesterol level, overweight, BMI, DM, glucose level, smoking, history of cerebrovascular disease and history of coronary heart disease) were not significantly associated with cognitive decline (Table 2). Moreover, the presence of multiple VRFs did not show a significant association with the annual rate of cognitive decline.

4. Discussion

In this cohort study with AD patients, we examined the influence of different and multiple VRFs (including HT, HC, DM, overweight and smoking) on the rate of cognitive decline measured as annual change in MMSE score. We found an association between both increasing age and increasing SBP, and a higher rate of cognitive decline.

Several studies researched the effect of age on cognitive decline in patients with AD. Sakurai et al. [6] performed a cohort study with 150 patients with AD and found more cognitive decline with increasing age ($\beta = 0.252$, $P = 0.002$). Other studies found no significant association [7–10].

Recently, a systematic review on the influence of VRFs on cognitive decline in patients with AD was published [3]. The results

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