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Blood pressure variability predicts cognitive decline in Alzheimer's disease patients

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ABSTRACT

The aim of our study was to evaluate whether blood pressure variability influences the rate of cognitive decline in Alzheimer's disease (AD). Two hundred and forty AD patients were periodically evaluated for a 12-month period. The blood pressure (BP) status of each patient was defined through mean and coefficient of variation for both systolic and diastolic BP. Progression of cognitive decline was investigated using the Mini Mental State Examination administered at entry and at the end of follow-up. Among the considered BP indices, only systolic BP variability explained the decrease in the Mini Mental State Examination score after adjustment for confounding variables (multiple linear regression: $R^2 = 0.603$, adjusted $R^2 = 0.513$; $p < 0.001$; logistic regression model: odds ratio = 2.882, 95% confidence interval = 1.772–4.495; $p < 0.001$). The receiver operating characteristic analysis for evaluating the ability of systolic BP variability to predict a faster cognitive decline presented an area under the curve of 0.913 (95% confidence interval = 0.874–0.953; $p < 0.001$). Our results suggest that BP variability may be added to the list of the potential vascular risk factors and included in the evaluation of AD patients to better define their risk profile.

1. Introduction

The relationship between vascular disease and cognitive impairment has been a matter of an on-going debate. In particular, hypotheses suggesting an additive or synergistic effect between cerebrovascular impairment and neurodegeneration have been developed (de la Torre, 2012). Few treatment options are available to improve the prognosis of patients with cognitive decline, and defining a role of vascular factors in the presentation and evolution of dementia would have important practical implications, as it would offer the opportunity of preventing, delaying, or slowing down the progression of cognitive dysfunctions by acting on them (de la Torre, 2002; Silvestrini et al., 2006, 2009; Viticchi et al., 2012). An increase in arterial blood pressure (BP) is the most important modifiable vascular risk factor, and it has been implicated in the promotion of cognitive decline (Luzzi et al., 2010). The concept that BP variability (BPV) may be more harmful than hypertension is a relatively recent notion (Rothwell, 2010). Accordingly, measures of variability in systolic BP (SBP) have been demonstrated as specific and powerful predictors of cerebral ischemic events (Rothwell et al., 2010). The aim of this study was to evaluate whether BPV influences the rate of cognitive decline in a group of patients with mild or moderate Alzheimer's disease (AD) during a 1-year follow-up period.

2. Methods

2.1. Participants

Patients were selected from consecutive subjects referred to the dementia outpatient service of the Neurological Clinic of Università Politecnica delle Marche by general practitioners for progressive cognitive impairment from January 2007 to June 2012. Inclusion criterion was a diagnosis of probable AD based on the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984). Patients were selected after a careful evaluation of clinical and instrumental exams by 2 neurologists with certified experience in managing patients with dementia.

Baseline age, sex, ethnicity, years of education, clinical history, and medications were obtained from all subjects via proxy- and self-report.

Brain magnetic resonance images were obtained for all patients using a 1.5-T scanner with the spin-echo technique and T1-weighted, T2-weighted, and fluid-attenuated inversion-recovery sequences to detect possible white matter lesions. These were

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graded according to Wahlund et al. (2001). Only patients without vascular lesions (grade 0) or with small subcortical focal lesions defined as high signal intensity areas on T2-weighted images, but isointense with normal brain parenchyma on T1-weighted images and classified as grade I were included. Patients with a clinical history of cardiovascular disease, stepwise progression of cognitive impairment, focal neurologic signs, severe subcortical leukoencephalopathy, cortical infarction, hemodynamically significant neck and large intracranial arteries stenosis or occlusion, and embolyzing cardiopathy, including atrial fibrillation were excluded. Furthermore, we excluded patients with major psychiatric pathologies and those with significant visual and hearing impairment.

2.2. Follow-up, blood pressure measurement, and cognitive assessment

Patients were followed-up for 12 months during which they received the acetylcholinesterase inhibitor donepezil (5 mg for 3 months and thereafter 10 mg/daily) in addition to the best therapy for each vascular risk factor. The pharmacologic treatment of vascular risk factors, in addition to behavioral recommendations (smoking cessation, regular physical exercise, and weight control), was planned in accordance with international guidelines (Goldstein et al., 2011; Leys et al., 2004). Every 3 months, from the beginning till the end of the follow-up period, each subject underwent a clinical evaluation to check the compliance to treatment and the possible occurrence of side effects of the treatment or medical conditions that could potentially influence the course of cognitive deterioration.

At baseline and at each follow-up clinic visit, BP was measured 3 times in the sitting position after 5 minutes rest using a standard mercury sphygmomanometer, and the mean of the second 2 readings was recorded. To characterize the BP status of each individual, mean (an average of values) and variability defined through the coefficient of variation (standard deviation [SD] $\times$ 100/mean) was obtained for both SBP and diastolic BP (DBP). Then, each patient was evaluated 5 times (baseline, at 3, 6, 9, and 12 months). At each time, 1 value for both DBP and SBP (the mean of the last 2 values) was obtained and used to obtain mean and SD values.

Progression of the cognitive decline was investigated using the Mini Mental State Examination (MMSE) administered at the entry and at the end of the follow-up period by a neuropsychologist blinded to the results of BP and BPV evaluations. A complete neuropsychological assessment was repeated at the end of the follow-up period to confirm the diagnosis of AD. Cognitive outcome was considered the difference between baseline and 12-months follow up MMSE scores.

2.3. Standard protocol approvals, registrations, and patient consents

The study was approved by the local ethical committee. All patients or caregivers included in the study gave written informed consent according to the Declaration of Helsinki.

2.4. Statistical analysis

Descriptive statistics were computed on the demographic data, comorbidities, actual medication, and vascular risk factors and were expressed as mean $\pm$ SD for continuous variables or as the number (%) of subjects for categorical variables. We also looked for colinearity between exposure variables with tolerance index and variance inflation factor. Because the aim of the study was to investigate whether and how severity of progression of cognitive decline could be related to BPV, this goal was best served by a regression model. Simple regression analyses were performed to firstly evaluate the bivariate association between the MMSE change (as a continuous measure) and BP mean and variability values. A multiple regression analysis was thus applied considering the potential confounding effect of demographic characteristics (sex, age, and education), body mass index, APOE genotype, baseline MMSE score, severity of dementia (mild vs. moderate) vascular risk factors (hypertension, diabetes, smoking habits, and hyperlipidemia), burden of white matter disease (grade 0 vs. 1 according with Wahlund scale) and treatments (antihypertensives, statins, antiplatelets).

Then, to provide additional information potentially useful for clinicians, cognitive variable outcome was divided into 2 groups: greater than or equal to (faster cognitive decline) and less than (slower cognitive decline) a decrease of 4 points on the MMSE. This cutoff value was chosen in accordance with a previous study (Weimera and Sager, 2009) whose results demonstrated that AD patients with a fast progression of cognitive decline presented a yearly reduction in MMSE score described by a uniform distribution yielding a mean value of 4 points. Moreover, a 4-point decrease may be reasonably regarded as large enough to exclude the possibility that it was because of an intrinsic limit of test reliability.

χ^2 test and 2-sample t test, as appropriate, were used to test differences at the $p < 0.05$ level on each of the subjects' characteristics. The risk of cognitive decline in relation to the BP indices was thus evaluated using a logistic regression model, adjusting for the effect of the potential confounding variables. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to quantify this effect.

Next, we performed a receiver operating characteristic analysis to evaluate the ability of BPV to predict a faster cognitive decline selecting the one with the highest Youden index as the cutoff point. SPSS 19.0 package for Windows was used for statistical analysis.

3. Results

A total of 267 Caucasian patients with mild to moderate probable AD were initially evaluated. Among them, 16 were excluded: 12 for cortical infarction or extensive white matter lesions, 3 for moderate to severe carotid stenosis or occlusion, and 1 for respiratory or cardiac problems. Of the remaining 251 patients, 9 were lost to follow-up (refused to come for further evaluation), whereas in 2 of them the diagnosis of the type of dementia was changed at the end of the follow-up period because clinical elements suggestive of dementia with Lewy bodies emerged.

The demographic characteristics, risk factors, treatments, and scores of the MMSE administered at baseline of the 240 patients who completed the study are reported in Table 1. No patient reported stroke or transient ischemic attack. There were neither any side effects of the drugs nor any intercurrent medical conditions, including those interfering with visual and hearing ability, which could potentially influence cognitive decline evolution during the follow-up period. According to simple regression analysis, MMSE change was associated to SBP variability (B = 0.421, 95% CI = 0.387–0.454; $p < 0.001$) and DBP variability (B = 0.123, 95% CI = 0.059–0.188; $p < 0.001$) and not to mean SBP (B = −0.008, 95% CI = −0.033 to 0.016; $p = 0.497$) and mean DBP (B = −0.006, 95% CI = −0.046 to 0.034; $p = 0.766$); multiple linear regression (Table 2) indicates that only SBP variability can explain the decrease in MMSE score (R = 0.776, $R^2 = 0.603$, adjusted $R^2 = 0.513$, $p < 0.001$) after adjustment for confounding variables with an annual rate reduction in MMSE by about 0.4 points for the unitary percentage increase in systolic BPV. Fig. 1 shows the point-to-point linear relationship between SBP and DBP variability and MMSE score change (SBP variability: R = 0.849, $R^2 = 0.720$; DBP variability R = 0.239, $R^2 = 0.057$).