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Longer Duration of Hypertension and MRI Microvascular Brain Alterations Are Associated with Lower Hippocampal Volumes in Older Individuals with Hypertension

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Abstract.
Background: Hippocampal atrophy is associated with cognitive decline. Determining the clinical features associated with hippocampal volume (HV)/atrophy may help in tailoring preventive strategies.
Objective: This study was aimed to investigate the association between HV (at visit 2) and vascular status (both at visit 1 and visit 2) in a cohort of individuals aged 60+ with hypertension and without overt cognitive impairment at visit 1 (visit 1 and visit 2 were separated by approximately 8 years).
Methods: Hippocampal volume was estimated in brain MRIs as HV both clinically with the Scheltens' Medial Temporal Atrophy score, and automatically with the Free Surfer Software application. A detailed medical history, somatometric measurements, cognitive tests, leukoaraiosis severity (Fazekas score), vascular parameters including pulse wave velocity, central blood pressure, and carotid artery plaques, as well as several biochemical parameters were also measured.
Results: 113 hypertensive patients, 47% male, aged 75.1 ± 5.6 years, participated in both visit 1 and visit 2 of the ADE-LAHYDE study. Age ($\beta = -0.30$) and hypertension duration ($\beta = -0.20$) at visit 1 were independently associated with smaller HV at visit 2 ($p < 0.05$ for all). In addition to these variables, low body mass index ($\beta = 0.18$), high MRI Fazekas score ($\beta = -0.20$), and low Gröber-Buschke total recall ($\beta = 0.27$) were associated with smaller HV at visit 2 ($p < 0.05$ for all).

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Conclusion: In a cohort of older individuals without cognitive impairment at baseline, we described several factors associated with lower HV, of which hypertension duration can potentially be modified.

Keywords: Aortic stiffness, brain MRI, cognitive decline, dementia, hippocampus, hypertension, macrovascular, microvascular, white matter lesions

INTRODUCTION

The hippocampus is a brain area with a crucial role in several memory functions. Hippocampal atrophy is one of the most typical anatomical and imaging findings of Alzheimer's disease (AD) [1]. Several reports, including a meta-analysis of 28 studies (789 patients), showed that hippocampal volume (HV) is associated with cognitive impairment [2]. Recently-developed automatic software has enabled the accurate, quick, and reliable assessment of HV from magnetic resonance imaging (MRI) [3, 4].

Identifying the risk factors associated with cognitive decline is relevant to design better prevention strategies; as HV is associated with cognitive impairment, identifying the factors associated with smaller HV may serve as an early surrogate for cognitive alterations. Increasing evidence suggests that long standing hypertension, diabetes, hypercholesterolemia, and overt vascular damage contribute to memory impairment and the pathogenesis of vascular dementia and AD. Although the exact underlying mechanisms remain unclear, vascular lesions may activate pathways leading to neurodegenerative lesions [5].

The aim of the present study was to investigate the association between vascular status and HV (between two visits separated by approximately 8 years), in older hypertensive subjects without overt cognitive impairment. HV was measured both clinically by Scheltens' Medial lobe Temporal Atrophy (MTA) score, and automatically with the use of the Free Surfer Software (FSS).

METHODS

Study population

The ADELAHYDE study was a prospective, longitudinal, single-center study, with two visits (visit 1, V1 and visit 2, V2) separated by approximately 8 years, investigating the role of vascular factors in the evolution of cognitive impairment and dementia in a cohort of elderly hypertensive patients. Inclusion criteria for ADELAHYDE were age 60–85 years with arterial hypertension (>1 year from diagnosis, receiving antihypertensive treatment for at least one month), presenting with low-grade subjective memory complaints (SMCs) defined as a McNair scale >15 (revised validated French version of 26 items). Patients were initially (V1) recruited in 2005 by local press advertisements or referral by general practitioners from an investigator network of the *Inserm Clinical Investigation Centre*. Patients initially included at V1 were contacted by telephone to participate in the second visit (V2) (conducted from April 2011 to November 2013). Of the 376 patients included in V1, 131 participated in V2 (among the rest, 51 patients died, 60 were lost to follow-up, 130 were not able to visit due to their functional status and/or refused to participate, and 6 patients provided no specific reason). This follow up participation rate, about 35%, is noticed also in other longitudinal epidemiological studies in elderly people, not only because of the high rate of mortality in these ages but mostly because of the important and accelerated functional and cognitive status impairment above the age of 65 [6, 7]. Finally, 113 of the 131 participants underwent an MRI examination and were included in the analysis. Further information on the study description is provided in previous publications [8] and at ClinicalTrials.gov (NCT01351961).

Vascular measurements and target organ damage assessment

Blood pressure was measured on the left arm, in the supine position, after a minimum 10-min rest, using a validated electronic device (DINAMAP 400Pro). Arterial stiffness was estimated by the gold standard methodology, pulse wave velocity (PWV), measured automatically by mechano-transducers, with the Complior device (Colson, Paris, France). Additionally, Augmentation Index was estimated by applanation tonometry in the radial artery (SphygmoCor Pulse Wave Analysis; PWV Medical Pty Ltd, Ermington, Sydney, Australia). Left ventricular hypertrophy (LVH) was defined by the presence of Sokolow-Lyon (>38 mm) and/or Cornell product (>2.44 mm*ms) indices on electrocardiogram

(ECG). Intima media thickness, as well as atheromatous plaques, were estimated in the common carotid arteries with ultrasonography (B mode system with a 7.5-MHz linear array transducer (ATL Apogee 800). Microalbuminuria was determined in 24-h urine collection samples [9].

Cognitive status assessment

Cognitive status was assessed based on performance in various psychometric tests. More specifically, McNair's Cognitive Difficulties Scale, the Geriatric Depression Scale, and the Free and Cued Selective Reminding Test (FCSRT) for immediate and delayed memory and language (free and cued recall) were performed by trained psychologists in both visits. Composite scores (Global memory test) were calculated for memory function (real memory score, including two components from the FCSRT: free [episodic memory] and cued [semantic memory] recalls), verbal fluency (which describes language lexical fluidity and includes four tests), and visual memory capacity (visual memory score, defining raw visual memory and errors with two tests). Each composite score was computed by transforming individual test scores into standardized z-scores (z-score ¼ test score-mean test score/ standard deviation [SD]). A higher value in the Global Memory Test reflected worse memory function.

Brain MRI imaging analysis

Brain imaging analysis was performed using brain MRI obtained with a 1.5 Tesla system (Signal General Electric; GEMS), performed in the axial and sagittal planes with a slice thickness of 5-mm. HV was estimated by two different methodologies, manually by an expert radiologist based on the MTA scale, known as Scheltens' score, and automatically with FSS [10]. Grading of the Scheltens' score includes a 5-stage escalation (0: no atrophy, 1: only widening of choroid fissure, 2: also widening of the temporal horn of lateral ventricle, 3: moderate loss of HV (decrease in height), and 4: severe loss of HV) [11]. Free Surfer software version 5.2 (http://surfer.nmr.mgh.harvard.edu/) was applied on high-resolution 3D-T1-weighted MR images to obtain HV for all subjects using an observer-independent approach. Hippocampal segmentations were based on a statistical atlas built primarily on ultra-high resolution (∼0.1 mm isotropic) *ex-vivo* MRI data. All HV (measured in mm^3) were standardized for total intracranial volume (TIV, measured in mm^3) by dividing on TIV in order to overcome the potential differences due to variations of cranial cavity size and height [3, 12]. In order to avoid excessive decimal places in the HV/TIV ratio, and to facilitate the readability of the manuscript, we multiplied this ratio by 1000. Notwithstanding, we also performed the analysis by adjusting HV on TIV within the models.

A white matter hypertrophy (WMH) grading was conducted using the T2-weighted axial images. The grading was performed as described in detail elsewhere [8], using the scale of Fazekas, accounting separately for periventricular lesions and deep white matter lesions (subcortical). According to the number of deep white matter and periventricular lesions, patients were divided into 3 groups (0-1, 2-3, and 4–6) [4, 13]. Both manual MRI evaluations (Fazekas scale and Scheltens' score) were performed by an experienced neuroradiologist blinded to the patients' clinical characteristics.

Genetic associations

Genotyping was performed in the context of a multimarker assay using an immobilized probe approach, as described previously [14] (Roche Molecular Systems, Alameda, CA, USA). In total, 10 AD-related genes/polymorphisms were extracted and included in the present analysis.

These genetic variables are expressed as categorical because alleles exist in each gene. For example, ApoE 112 has cysteine and arginine as allele. So, the combination of alleles in this gene are cysteine-cysteine, cysteine-arginine, and arginine-arginine.

Statistical analysis

For continuous variables, results are presented as mean ± standard deviation, while non-parametric tests results are presented as median (percentile$_{25–75}$); categorical variables are presented as numbers (n) and proportions (%). HV was divided by the median value in below versus above the median to obtain similar proportion of patients within each subgroup. Student *t*-test or Mann–Whitney test was used to estimate differences in mean values between two groups (above versus below the median) if the distribution of the variables was normal or skewed, respectively. One-way ANOVA with Tukey *post-hoc* test for the correction for multiple comparisons when the groups were

three or more. Analysis of qualitative variables was carried out by the Chi-square test. To explore the relationship between HV and Scheltens' score with target organ damage and cardiovascular risk factors while controlling for other covariates, both linear multivariate analyses, with the enter method, and logistic multivariate analysis models were applied, respectively. All variables with $p < 0.15$ in univariate analysis were included in the multivariate models. A p value < 0.05 was considered statistically significant. All analyses were performed with STATA version 16.

The data will be available to other researchers upon request with a detailed hypothesis and Statistical Analysis Plan (SAP) addressed to Pr. Athanase Benetos (a.benetos@chru-nancy.fr).

RESULTS

Characteristics of study patients

In total, 113 subjects, 46% male, aged 75.1 ± 5.6 years, had MRI brain images and were included in the present analysis. Baseline characteristics of the study population are summarized in Table 1. According to Scheltens Score classification, 53% ($n = 60$) of participants had no atrophy (stage 0), 31% ($n = 35$) had only widening of choroid fissure (stage 1), and 16% ($n = 18$) had widening of the temporal horn of the lateral ventricle or greater (stage 2). Male patients had significantly smaller HV/TIV(*1000) assessed by FSS than females (2.54 versus 2.71, $p = 0.017$).

Visit 1 predictors of hippocampal volume at visit 2

Male sex ($\beta = -0.26$), age ($\beta = -0.30$), and hypertension duration ($\beta = -0.20$) at visit 1 were associated with smaller HV (divided by the TIV) at visit 2 ($p < 0.05$ for all). The total model was able to explain 22% of the variation in HV (Table 2, Fig. 1). The associations of the HV adjusted on the TIV (instead of divided) remained similar to those above described, except for male sex, that lost statistical significance (Supplementary Table 2).

Associations of hippocampal volume at visit 2

Older age ($\beta = -0.24$), male sex ($\beta = -0.22$), lower body mass index (BMI; $\beta = 0.18$), longer history of hypertension ($\beta = -0.20$), higher Fazekas score ($\beta = -0.20$), and a reduced Cognitive Test Score ($\beta = 0.27$), were all associated with smaller HV. The total model was able to explain 39% of the variation in HV (Table 3). Similarly, to the above described, the associations of the HV adjusted on TIV (instead of divided) remained similar to those above described, except for male sex, that lost statistical significance and BMI that showed only a tendency toward lower HV (Supplementary Table 3). Regarding the Scheltens score, in the multivariate logistic regression model, all MRI variables (Fazekas scale and HV estimated by FSS) were associated with it, independently of the other clinical factors. In the model without the MRI variables, increased age and worse memory function also remained statistically significant predictors of an increased Scheltens' score (Supplementary Table 4).

All factors significantly associated with impaired HV are depicted in Fig. 2.

The arterial parameters measured at the baseline assessment of the patients (at V1) were also analyzed, as shown in Supplementary Table 1. Apart from older age, male gender, and long hypertension duration, none of the cognitive status tests performed at V1 were significantly correlated with HV and only the baseline Fazekas risk score showed a tendency to be associated with lower HV ($p = 0.069$).

No statistically significant difference was found between the change (delta) of cardiovascular risk factors between Visit 1 and 2 and HV (Supplementary Table 5).

Genetic associations with hippocampal volume

In our study, among 113 patients, 81 had cysteine-cysteine, 28 had cysteine-arginine, and 4 had arginine-arginine alleles. None of these alleles was associated with HV (Supplementary Table 6).

DISCUSSION

This study aimed to investigate the association between vascular status and HV, in older hypertensive subjects without overt cognitive impairment. The most important findings of the study were: 1) long duration of hypertension and small vessel disease quantified in MRI with the Fazekas score were independently associated with lower HV; 2) cognitive function scores could predict HV only when performed at the same time with MRIs and not in the past (i.e., 8 years ago), highlighting the importance of the continuing clinical assessment of elderly patients, even if they were in a relatively good cognition in the past.

Table 1
Characteristics of the study population undergoing visit 2 of the ADELAHYDE study, according to median hippocampal volume measured with the Free Surfer Software (adjusted for total intracranial volume)

Population characteristics	Total	Hippocampal volume[a] (median)		*p*-value
	$n = 113$	<2.7 ($n = 57$)	≥2.7 ($n = 56$)	
Socio-demographic parameters				
Female gender, *n* (%)	61 (54.0)	27 (47.4)	34 (60.7)	0.15
Age (years)	75.1 ± 5.6	76.5 ± 5.5	73.7 ± 5.3	0.005
Intermediate/high education level, *n* (%)	81 (71.7)	39 (68.4)	42 (75.0)	0.44
Risk and hemodynamic factors				
Past/current smoker, *n* (%)	44 (38.9)	23 (40.4)	21 (37.5)	0.76
BMI (kg/m²)	27.8 ± 4.8	27.4 ± 4.3	29.9 ± 4.9	0.007
SBP (mmHg)	140.9 ± 17.7	140 ± 16	142 ± 19	0.55
DBP (mmHg)	72.9 ± 9.5	72 ± 9	74 ± 9	0.40
Pulse pressure (mmHg)	68.0 ± 13.4	68 ± 12	68 ± 14	0.83
Heart rate (bpm)	62.1 ± 9.5	63 ± 9	65 ± 10	0.24
(Laboratory work-up, Biochemical examinations)				
MDRD eGFR (ml/min/1.73m^2)	70.3 ± 15.7	69 ± 16	71 ± 15	0.47
Sodium (mmol/L)	140.1 ± 2.1	139.8 ± 2.5	140.3 ± 1.7	0.23
Total cholesterol (g/L)	2.02 ± 0.4	2.05 ± 0.43	1.95 ± 0.41	0.28
LDL cholesterol (g/L)	1.19 ± 0.34	1.22 ± 0.35	1.16 ± 0.33	0.33
HDL cholesterol (g/L)	0.57 ± 0.15	0.59 ± 0.14	0.56 ± 0.15	0.31
Homocysteine (mmol/L)*	15.3 (12.5–17.1)	15.6 ± 4.5	15.0 ± 5.1	0.53
C-reactive protein (mg/L)*	2.1 (1–4.9)	1.6 (0.8–4.8)	3.1 (1.4–5.3)	0.11
Medical history				
Hypertension duration (years)*	20.8 ± 8.1	22.5 (15–27)	18.0 (13–24)	0.050
Diabetes, *n* (%)	19 (16.8)	7 (12.3)	12 (21.4)	0.19
HbA1c (%)	6.1 ± 1.04	5.9 ± 1.0	6.2 ± 1.1	0.11
History of vascular events				
– myocardial infarction	18 (15.9)	11 (19.3)	7(12.5)	0.32
– stroke	4 (3.5)	2 (3.5)	2 (3.6)	0.99
– transient ischemic attack	6 (5.3)	2 (3.5)	4 (7.4)	0.36
Medications				
ACEi/ARBs, *n* (%)	81 (71.7)	41 (71.9)	40 (71.4)	0.95
Beta-blockers, *n* (%)	37 (32.7)	17 (29.8)	20 (35.7)	0.51
CCB, *n* (%)	41 (36.3)	21 (36.8)	20 (35.7)	0.90
Diuretics, *n* (%)	57 (50.4)	29 (50.9)	28 (50.0)	0.93
Statins, *n* (%)	64 (56.6)	32 (56.1)	32 (57.1)	0.91
Antithrombotic agents, *n* (%)	22 (19.5)	17 (29.8)	5 (8.9)	0.005
Paraclinical investigations and psychometric assessment				
Gröber-Buschke test:				
– free recall	25.6 ± 8.6	22.1 ± 9.6	28.6 ± 6.8	<0.001
– total recall (free and cued)	46 (42–48)	43 (40–47)	47 (45.5–48)	<0.001
– composite score (“global memory”)	1.1 ± 1.3	1.4 ± 1.3	0.7 ± 1.2	0.004
Target organ damage				
Intima-media thickness (mm)	0.72 ± 0.23	0.73 ± 0.22	0.72 ± 0.24	0.94
Carotid atheromatous plaque, *n* (%)	30 (26.5)	16 (29.1)	14 (25.5)	0.67
Pulse wave velocity (m/s)	12.3 ± 3.9	12.6 ± 4.1	12.0 ± 3.7	0.45
Augmentation index (%)	38.2 ± 18.6	37.3 ± 14.8	39.0 ± 21.7	0.64
LV hypertrophy on ECG, *n* (%)	16 (14.2)	7 (12.5)	9 (16.4)	0.56
Microalbuminuria (mg/L)*	9.4 (3.7–19.2)	9.2 (4.1–17.5)	9.7 (3.4–25.1)	0.95
MRI Fazekas Score				
0–3 scale in categories, *n* (%)	70 (61.9)	30 (52.6)	40 (71.4)	0.040
4–6 scale in categories, *n* (%)	43 (38.1)	27 (47.4)	16 (28.6)	
MRI Scheltens’ score, *n* (%)				
0	59 (52.7)	19 (33.9)	40 (71.4)	<0.001
≥1	53 (47.3)	37 (66.1)	16 (28.6)	

For continuous variables, results are presented as mean ± standard deviation while *non-parametric tests results are presented as median (percentile$_{25–75}$); categorical variables are presented as numbers (n) and proportions (%). [a]Values of hippocampal volume have been calculated by the division of HV in mm^3 by the total intracranial volume (mm^3) and multiplied by 1000. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LV, left ventricular; ECG, electrocardiogram; MDRD, modified of diet in renal disease equation 4; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; CCB, calcium channel blockers; MRI, magnetic resonance imaging.

Table 2
Linear regression multivariate model to determine the factors at visit 1 associated with hippocampal volume at visit 2 assessed with FSS

Hippocampal volume	B	95% CI	*p*
Visit 1			
Overall model fit (Adj. $R^2 = 0.22$)	–	–	<0.001
Constant	4.5	3.7 to 5.3	<0.001
Gender (male versus female)	–0.20	–0.33 to –0.07	0.002
Age (per each 10 y)	–0.25	–0.37 to –0.13	<0.001
Hypertension duration (y)	–0.01	–0.02 to –0.01	0.039

FSS, Free Surfer Software; BMI, body mass index; MRI, magnetic resonance imaging. Values of hippocampal volume have been calculated by the division of HV in mm^3 by the total intracranial volume (mm^3) and multiplied by 1000.

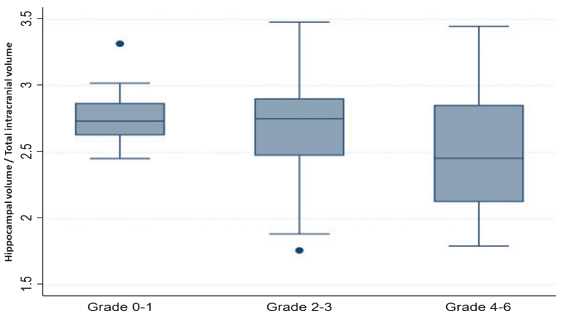

Fig. 1. Hippocampal volume assessed with Free Surfer Software according to Fazekas scale (grade, category). y axis, hippocampal volume (average of left plus right hippocampal volume in mm^3) divided by the total intracranial volume (in mm^3) multiplied by 1000; x axis, Fazekas grade. Multiple-comparison adjusted *post-hoc* test: Grade 0-1 versus Grade 2-3, $p = 0.50$; Grade 0-1 versus Grade 4–6, $p = 0.031$; Grade 2-3 versus Grade 4–6, $p = 0.008$.

Our results show that only the duration of hypertension (and not the blood pressure levels) were positively correlated (and "predicted" HV), after considering other risk factors. Studies on the effect of blood pressure levels on cognitive status suggest that midlife BP measurements are much better correlated with cognitive decline than late-life BP measurements. While it is evident that hypertension is one of the most powerful modifiable risk factors for cerebral diseases, most of the studies refer to strokes, with fewer referring to vascular dementia and only a few recent studies have suggested an effect on the progression of AD [15–17]. More specifically, patients with distinctive, pathophysiological alterations of AD (i.e., neurofibrillary tangles and an increased number of neuritic plaques in the entorhinal cortex and hippocampus) as well as total brain atrophy have been found to have elevated blood pressure [18, 19]. This may be due to the fact that blood pressure tends to decrease in the years before dementia diagnosis such that individuals with severe dementia tend to have lower blood pressure than earlier in life and lower blood pressure values than their pairs without dementia [20, 21]. Thus, the duration of hypertension in our population reflects the chronic, cumulative burden of hypertension. Similarly, the microvascular lesions of the white matter quantified in MRI with the Fazekas score also reflect the chronic burden of vascular alterations on the brain. These results are in accordance with data showing that hippocampal atrophy is mainly the result of a chronic rather than acute hypoperfusion [22].

Regarding the other subclinical indices of target organ damage in our study (microalbuminuria, intima-media thickness (IMT), LVH, and arterial stiffness), none of the latter correlated with any of the hippocampal variables. With regards to IMT, data from the Framingham Study showed that neither carotid stenosis nor IMT was associated with HV, suggesting that the association of carotid atherosclerosis with cognitive decline could not be explained by neurodegenerative "AD type" brain changes of the hippocampal area [23]. Experimental models in aged rats with carotid stenosis [24] furthermore showed that only severe carotid artery stenosis, resulted in a significantly lower number of surviving cells in the hippocampal region. Data from the Strong Heart Study on the relationship between LVH and HV previously showed that higher LVM in midlife was associated with a slightly lower general cognitive performance and smaller HV in later life. However, this study had major methodological limitations, since LVH was evaluated only in the first visit and HV only in the second visit (17 years later) [25].

In our study, PWV did not significantly differ between those with a larger versus those with a smaller hippocampus. Nonetheless, it has been documented that patients with increased PWV may have impaired cognitive status later in life [26–29].

Table 3
Linear regression multivariate model in determining the factors at visit 2 associated with hippocampal volume also at visit 2

Hippocampal volume	B	95% CI	*p*
Visit 2			
Overall model fit (Adj. $R^2 = 0.39$)	–	–	<0.001
Constant	3.10	2.10 to 4.10	<0.001
Gender (male versus female)	–0.17	–0.29 to –0.05	0.009
Age (per each 10 y)	–0.16	–0.27 to –0.05	0.004
BMI (Kg/m^2)	0.01	0.01 to 0.03	0.025
Hypertension duration (y)	–0.01	–0.02 to –0.01	0.014
MRI Fazekas Score	–0.05	–0.10 to –0.02	0.018
Gröber-Buschke: Total Recall (Free & Cued)	0.02	0.01 to 0.03	0.002

BMI, body mass index; MRI, magnetic resonance imaging. Values of hippocampal volume have been calculated by the division of HV in mm^3 by the total intracranial volume (mm^3) and multiplied by 1000.

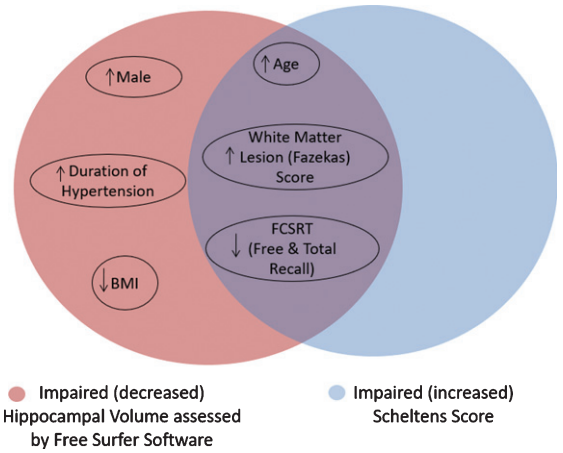

Fig. 2. Statistically significant factors correlating with decreased hippocampal volume assessed by Free Surfer Software and Scheltens' score.

In the present study, BMI in visit 2, independently of the other covariates, was positively correlated with HV. However, these results were not confirmed for BMI measured 8 years earlier during visit 1. Most of the studies investigating the relationship between HV and BMI show a consistent negative correlation for both midlife and late-life BMI [30, 31, 31, 32], implying that the noxious effects of obesity may start long before the clinical signs of dementia. A significant correlation only during late life between BMI and HV was also reported in another study investigating the relationship between BMI and while matter lesions, thus supporting that late-life BMI, as in the present our data, is seemingly the most relevant of the two. Moreover, similarly to the reduction in blood pressure, it has been shown that metabolic changes and a reduction in BMI precede the diagnosis of dementia [33, 34]. Similarly, data showing that late life BMI is inversely associated with CSF AD biomarkers and pathological findings in postmortem brains of AD [6, 35] Hence, the relationship between BMI and HV could be due to greater weight loss in those having a smaller hippocampal size.

Our results also suggest that the associations between the arterial factors and HV (and cognitive decline or WMH) are not genetically driven, at least by the genes we investigated.

In our population, cognitive tests performed in Visit 2 (Gröber-Buschke and Global Memory Test) were also associated with HV, independently of the other cardiovascular risk factors, thus confirming previous observations that hippocampal atrophy is associated with cognitive impairment [36, 37]. However, the assessment of cognitive status performed 8 years earlier (during visit 1) was not associated with future HV as measured in visit 2. These results are similar to those of a recently published study showing a limited role of baseline cognitive evaluation in the assessing the progression of MCI to AD over 5 years, in patients which had large HV in the baseline visit [38] further emphasizing the need for particular vigilance by physicians for repeated cognitive status assessment in older hypertensive patients.

Strengths and limitations

Several limitations must be acknowledged in the present study. The most important limitation of our study is the absence of hippocampal and medial temporal atrophy measurements during the first visit, to be able to evaluate the progression of HV, in parallel with the change(s) in vascular and cognitive factors, occurring over time. Moreover, there was a high "attrition"/lost to follow-up in this cohort which limits the power and precision of our findings. The

small sample size also precludes from retrieving more information of the data (e.g., regarding subgroups and/or genetic analyses). The FSS was used as a fully automatic tool and manual edits were not implemented. The FSS estimates of the temporal areas (such as entorhinal cortex) have a tendency to overestimate the HV. Moreover, FSS estimates of the temporal areas may be age-biased due to temporal horn widening. Adjusting the HV to the TIV (rather than dividing by it), led to a slight loss of statistical power due to the dispersion of the adjustment variables, however the final models remained stable and only sex lost statistical significance.

Conclusion

In a cohort of older individuals with hypertension and low-grade subjective memory complaints, older age, lower BMI, white matter lesions, cognitive impairment, and hypertension duration were found to be independent determinants of smaller HV. Whether preventive strategies (e.g., blood pressure control) could delay or even reverse potential hippocampal atrophy (and cognitive decline) requires further investigation.

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Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-0842r3).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-190842.

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