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Increased risk of cognitive impairment and more severe brain lesions in hypertensive compared to non-hypertensive patients with cerebral small vessel disease

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Although cerebral small vessel disease (SVD) is traditionally associated with aging and hypertension (HT), there are patients exhibiting sporadic SVD, free of HT. We aimed to investigate the differences in clinical and neuroradiological presentation in SVD patients in reference to the presence of HT as a risk factor (RF). Vascular RF, cognitive and functional status were evaluated in a cohort of 424 patients. Patients were classified in two groups based on the presence of HT. Severity of vascular lesions was assessed using 1.5 T magnetic resonance imaging with Age-Related White Matter Changes scale total score (tARWMC) and Fazekas scale periventricular (PV) and deep subcortical (DS) scores. No difference between groups in age and sex distribution was noted. In univariate analysis, HT was associated with vascular cognitive impairment (vCI) (OR 2.30, 1.53-3.45, $P < 0.0001$), functional status (OR 1.47, 1.11-1.95, $P = 0.007$), depression (OR 2.13, 1.23-3.70, $P = 0.007$), tARWMC (OR 1.10, 1.05-1.16 95% CI, $P < 0.0001$), Fazekas PV score (OR 1.34, 1.08-1.67 95% CI, $P = 0.008$), Fazekas DS score (OR 1.95, 1.44-2.63 95% CI, $P < 0.0001$) and total number of lacunes (OR 1.10, 1.02-1.18 95% CI, $P = 0.009$). Multivariate logistic regression analysis indicated that HT was an independent RF for vCI (OR 1.74, 1.09-2.76 95% CI, $P = 0.020$) and higher Fazekas DS score (OR 1.57, 1.11-2.22 95% CI, $P = 0.011$). The Kaplan-Meier curve of estimates of survival of SVD patients without vCI revealed a higher proportion of patients with HT progressing to vCI over time when compared to HT-free cases. In patients with sporadic SVD, HT is a contributing factor to worse clinical outcomes and neuroradiological presentation.

1 | INTRODUCTION

Cerebral small vessel disease (SVD) is well-recognized as an important cause of stroke and dementia, in particular in the aging population.[1,2] Clinical presentations of SVD are numerous and can range from asymptomatic cases with only magnetic resonance imaging (MRI) evidence of the disease to overt lacunar stroke, vascular dementia and late-onset depression.[2–4] Neuroradiological correlates of SVD are also diverse and comprise lacunes, confluent white matter hyperintensities (WMH), cerebral microbleeds and brain atrophy.[1,5–8] SVD tends to progress over time at least in a subpopulation of patients, leading to cognitive deterioration and functional dependency.[4,9,10]

Small vessel disease is typically attributed to common vascular risk factors (RF), most frequently advanced age and hypertension (HT).[1,11,12] The most prevalent form of SVD is age-related or hypertensive SVD, mainly characterized by functional and structural changes in the arterial vessel wall secondary to atherosclerosis, although mechanisms that link SVD with parenchyma damage are heterogeneous and not completely ellucidated.[13–16] Although often used,

the term hypertensive arteriopathy may be misleading, since it is not necessary related to HT, there is no consensus on its histological characteristics, and it underestimates the importance of other potential factors in the initiation and progression of SVD.[17] High blood pressure (BP) precedes SVD in a vast majority of patients but series of patients with typical SVD free of HT have been reported occasionally.[18,19]

We aimed to investigate the influence of HT on the clinical and neuroradiological presentation in our dataset of patients with sporadic SVD, followed up prospectively for signs of cognitive deterioration.

2 | METHODS

2.1 | Patient selection and evaluation

A cohort of consecutive patients initially presenting with TIA or minor stroke of the lacunar type, normal cognitive status and MRI evidence of SVD, was followed up and reassessed for cognitive decline at a mean period of 4 years after initial presentation. In all participants demographic data and vascular RF were assessed as well as functional status with the use of modified Rankin Scale (mRS) score, as previously reported.[9] Standard neuropsychological evaluation was used and patients meeting the NINDS-AIREN criteria for vascular dementia and criteria for cognitive impairment (CI)-no dementia were analyzed jointly as the vascular CI (vCI) group.[9] Patients were classified as depressed if the DSM-IV criteria for depressive disorder were met.[20]

A diagnosis of HT was established when systolic BP was ≥140 mm Hg and/or diastolic BP ≥ 90 mm Hg according to serial daily measurement (three times per day, as the standard procedure) in an in-patient setting and/or based on previous medical records, or if there was data on medical treatment of BP. Antihypertensive treatment was conducted per current guidelines and under the supervision of a clinical cardiologist.[21] Only patients who remained non-HT during the follow-up period were classified as HT-free cases. Clinical and MRI data were compared between HT and non-HT patients. The study was approved by the Ethics Committee of the Clinical Center of Serbia.

2.2 | Magnetic resonance imaging and image analysis

A trained neurologist blinded to clinical data applied two visual rating scales on T2-weighted axial scans performed on all participants at the baseline on a 1.5-T scanner (Siemens Avanto, Siemens AG, Berlin, Germany).[9] Overall burden of SVD was assessed with the use of total Age-Related White Matter Changes (tARWMC) scores, which were initially obtained for each brain region (frontal, parieto-occipital, temporal, basal ganglia and infratentorial) of both hemispheres and then summed for the whole brain (score range 0-30).[22] The visual rating scale of Fazekas was used to assess periventricular (PV) and deep subcortical (DS) WMH (score range 0-3).[23]

2.3 | Statistical analysis

Normality of data distribution was tested using the Kolmogorov-Smirnov test. Statistical analysis included analysis of variance (ANOVA) for continuous variables and the χ^2 test or Fisher exact test for categorical variables. Univariate logistic regression hazard analysis was used to compare data on clinical and MRI characteristics between groups in relation to the presence of HT. Multivariate logistic regression analysis was applied to identify independent parameters associated with HT, with risks shown as an odds ratio (OR), estimated for each selected variable with a 95% confidence interval (95% CI). Cox regression analysis was used to assess the influence of HT on vCI. Spearman rank correlation coefficient was used for the assessment of relationships between cognitive impairment and type of SVD lesions (tLI, Fazekas PV and DS scale scores) both in HT and HT-free patients. A value of $P < 0.05$ was considered statistically significant.

3 | RESULTS

A total of 424 patients with SVD were included in the study, 80 without and 344 with HT. During the follow-up period, only three patients initially classified as non-HT developed HT, and they were excluded from further analysis.

The hypertensive and non-HT patient subgroups did not differ in age, gender or education, with the mean age of the whole group being 62 (Table 1). Distribution of vascular RF, except for HT is shown in Table 1. The most frequent RF in both subgroups were hyperlipidemia, smoking, and diabetes. No difference between RF frequency or mean total number of RF was noted between groups (Table 1). The most frequent type of lacunar stroke syndrome was pure motor stroke (233 or 54.96% of total patients; 125 in HT, 108 in non-HT group), followed by sensorimotor stroke (96 or 22.64%; 50 HT, 46 non-HT), pure sensory stroke (56 or 13.21%; 26 HT, 30 non-HT), ataxic hemiparesis (16 or 3.77%; 7 HT, 9 non-HT), dysarthria-clumsy hand syndrome (13 or 3.07%; 7 HT, 6 non-HT) and atypical lacunar syndromes (10 or 2.35%; 4 HT, 6 non-HT). No difference was noted in lacunar syndrome distribution between HT and non-HT patients ($P = 0.796$).

There was no difference in the number of months to cognitive follow-up between groups (HT-free 46.1 ± 7.0, HT-patients 47.5 ± 7.0, whole group 47.3 ± 7.0, $P = 0.107$).

Compared to HT-free patients, those with HT had higher mRS scores, but overall disability was mild with a mean mRS of 2 (range 0-3) (Table 2). Patients with HT were more frequently diagnosed with vCI and depression, as compared to HT-free cases (Table 2). All MRI parameters indicating severity of WMH, comprising tARWMC, Fazekas PV and DS scores and the total number of lacunar infarcts were increased in SVD patients with HT, as compared to the HT-free group (Table 2).

Univariate logistic regression analysis adjusted for age and sex, showed that HT significantly correlated with the presence of vCI, the mRS score, a diagnosis of depression and the severity of WMH (Table 3).

TABLE 1 Demographic data and vascular RF distribution

	HT-free patients (n = 80)	HT patients (n = 344)	All patients (n = 424)	*P*-value[a]
Age (years)	62.4 ± 9.0	61.8 ± 10.3	61.9 ± 10.1	0.626
Male sex	42 (52.5)	181 (52.6)	223 (52.6)	0.985
Education, years	11.9 ± 1.7	12.0 ± 2.3	12.0 ± 2.2	0.565
Diabetes mellitus	21 (26.3)	80 (23.3)	101 (23.8)	0.571
Hypercholesterolemia	58 (72.5)	279 (81.1)	337 (79.5)	0.086
Smoking	32 (40.0)	116 (33.7)	148 (3.49)	0.289
CAD	10 (12.5)	49 (14.2)	59 (13.9)	0.685
PAD	6 (7.5)	23 (6.7)	29 (6.8)	0.795
AF	6 (7.5)	26 (7.6)	32 (7.5)	0.986
Carotid stenosis >50%	4 (5.0)	22 (6.4)	26 (6.1)	0.639
Total number of RF	1.7 ± 1.0	1.7 ± 1.1	1.7 ± 1.1	0.953

Data are given as n, % or mean ± SD.
AF, atrial fibrillation; CAD, coronary artery disease; HT, hypertension; PAD, peripheral artery disease; RF, risk factors.
[a]*P*-value is given for the difference between subgroups.

TABLE 2 Clinical and neuroimaging characteristics of patient subgroups

	HT-free patients (n = 80)	HT patients (n = 344)	All patients (n = 424)	*P*-value
mRS	1.7 ± 0.8	2.0 ± 0.9	1.9 ± 0.9	0.008
vCI	26 (32.5)	201 (58.4)	227 (53.5)	<0.0001
Depression	20 (25.0)	143 (41.6)	163 (38.4)	0.006
tARWMC scale score	10.5 ± 4.5	13.1 ± 5.7	12.6 ± 5.6	<0.0001
Fazekas PV score, median (range)	1 (0, 3)	2 (0, 3)	2 (0, 3)	<0.0001
Fazekas DS score median (range)	2 (1, 3)	3 (0, 3)	3 (0, 3)	<0.0001
Number of lacunar infarcts	7.9 ± 3.1	9.1 ± 3.9	8.9 ± 3.8	0.008

Data are given as n, % or mean ± SD unless stated otherwise.
DS, deep subcortical; HT, hypertension; mRS, modified Rankin Scale; PV, periventricular; tARWMC score, total Age-Related White Matter Changes score; vCI, vascular cognitive impairment.

Multivariate logistic regression analysis revealed that the presence of HT was independently associated with vCI (OR 1.74, 1.09-2.76 95% CI, $P = 0.020$) and the Fazekas DS score (OR 1.57, 1.11-2.22 95% CI, $P = 0.011$).

Cox regression analysis, adjusted for all significant confounders (tARWMC, Fazekas PV and DS scale scores, number of lacunes, depression and mRS) showed that the presence of HT was associated with an HR of 1.60 (1.16-2.21 95% CI, $P = 0.004$) for vCI.

For the HT group, correlations between vCI and severity of DS lesions on Fazekas scale (Spearman's $r = 0.526$, $P < 0.0001$) and severity of PV lesions on Fazekas scale ($r = 0.467$, $P < 0.0001$), were stronger compared to correlation between vCI and tLI ($r = 0.198$, $P = 0.0002$). In non-HT patients, strongest correlation was detected between vCI and PV lesions on Fazekas scale ($r = 0.528$, $P < 0.0001$), followed with tLI ($r = 0.390$, $P = 0.0003$) and DS lesions ($r = 0.322$, $P = 0.004$).

Figure 1 shows a Kaplan-Meier curve of estimates of survival of SVD patients without vCI over follow up time in relation to the presence of HT as a RF, indicating a higher proportion of patients with HT progressing from normal cognitive status to cognitive decline over time, as compared to HT-free patients.

4 | DISUSSION

In our dataset of patients with sporadic cerebral SVD, the presence of HT was associated with a more severe clinical and neuroradiological presentation, as compared to HT-free cases. In particular, when adjusted for all significant confounders including the severity of vascular brain lesions, functional status and depression, the presence of HT was associated with an increased risk for cognitive decline, with an HR of 1.60.

TABLE 3 Variables associated with HT, adjusted by age, sex and education; univariate logistic regression analysis

	OR (95% CI)	*P*-value
vCI	2.30 (1.53-3.45)	<0.0001
mRS	1.47 (1.11-1.95)	0.007
Depression	2.13 (1.23-3.70)	0.007
tARWMC scale score	1.10 (1.05-1.16)	<0.0001
Fazekas PV score	1.34 (1.08-1.67)	0.008
Fazekas DS score	1.95 (1.44-2.63)	<0.0001
Number of lacunes	1.10 (1.02-1.18)	0.009

DS, deep subcortical; mRS, modified Rankin Scale; PV, periventricular; tARWMC score, total Age-Related White Matter Changes score; vCI, vascular cognitive impairment.

Traditionally, HT has been considered the strongest vascular RF for SVD and vCI.[24–26] Increased BP and HT were significantly related to impaired microstructural integrity not only in ischemic WMH but also in normal-appearing white matter.[27] Furthermore, high BP, diastolic in particular, has been identified as an independent predictor of SVD progression in longitudinal studies.[28–32] Nevertheless, the role of HT in SVD pathogenesis is rather complex, with many patients with lacunar stroke being normotensive, and HT being equally common in non-lacunar stroke as in lacunar.[33] There are indications that high BP does not contribute to lesion progression in people with already severe lesions at baseline, nor in the very old.[31] In our dataset, hypertensive SVD patients had more pronounced cerebral lesions, comprising a total score of SVD burden (tARWMC), PV and DS lesions as well as higher number of LI on imaging when compared to the non-HT subgroup, after adjusting for age and sex. More severe cerebral vascular lesions in HT SVD patients were associated with more functional disability, both in our and in previous reports.[19]

In our cohort, no difference in RF distribution was noted between hypertensive and HT-free cases, which is in accordance with other reports.[34,35] The other most frequent RF in both of our subgroups were hyperlipidemia, smoking and diabetes. An older age (85+) and male gender were previously reported to be independently associated with lacunar infarction in non-hypertensive patients, with diabetes mellitus being the leading RF.[19] Every fourth non-HT SVD patient in our group had diabetes, which corresponds to the previously reported range of 11%-38%.[19,36,37] Notably, non-HT SVD patients in our cohort had showed significant clinical impairment, with every fifth patient showing evidence of vCI and every fourth signs of depression.

The presence of HT increased the risk of both vCI and depression twofold in our cohort. HT has been associated with the development of both degenerative and vascular dementia with a range of mechanisms suggested, including development of SVD pathology, reduced brain volume and cortical thickness, reduced white matter microstructural integrity, alterations of cerebral autoregulation and promoting of endothelial dysfunction.[17,26,38] However, there are conflicting results indicating an increased risk with midlife HT and reversed association for old age HT.[39] We found strong association between HT presence and all parameters of brain lesion severity, DS WHM in particular but it is important to note that our SVD group mean age was 61, which is probably the result of tertiary institution referral. In a longitudinal study, Uiterwijk and co-workers noted that in patients with HT, it was not the severity of baseline lesions but the progression of PV WMH over 4 years which was associated with cognitive decline, emphasizing the importance of preventing the progression of WMH in hypertensive patients.[25] HT has been also associated with vascular or late-onset depression, but this relationship is bidirectional and complex.[40–43] Both depressive symptoms and apathy are frequent in SVD patients, are associated with MRI lesions, and also contribute to the risk of cognitive decline.[44,45]

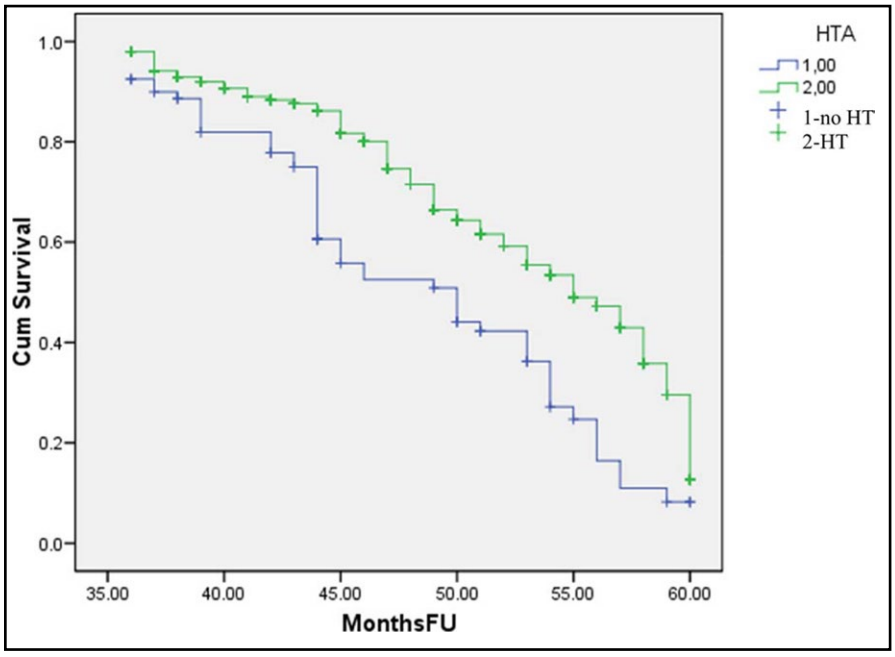

FIGURE 1 Kaplan-Meier curve of estimates of survival of SVD patients without cognitive decline (*y* axis) over time of follow up (in months) (*x* axis) in relation to presence of HT as RF; line 1 represents patients without HT, line 2 represents patients with HT

There are other factors that may contribute to HT-related cerebral damage, such as increased 24-hour BP variability or amyloid cascade activation.[32,46,47] It has even been suggested that hypertensive and non-hypertensive patients with WMH might have different underlying pathologies with differences in genetic architecture.[48] In subjects of the Lothian Birth Cohort 1936, vascular RF explained 70% of the large artery disease variance but only 1.4%-2% of WMH variance, suggesting a non-vascular and non-atheromatous background of the SVD at least in a subpopulation of patients.[49] This finding may explain the limited effect of RF modifications on preventing WMH progression.[33]

As many as half of the patients with first-ever lacunar infarct have mild cognitive impairment of the frontal-subcortical type.[50–52] Grau-Olivares and co-workers reported vCI in 23/40 patients with lacunar stroke, 1 month after the qualifying event, arguing that neuropsychological impairment should be considered as a common clinical feature in acute lacunar infarction.[50] In the SPS3 study, 47% of patients had mild cognitive impairment when assessed within 6 months of their first-ever small subcortical stroke, with the largest deficits detected on tests of episodic memory, verbal fluency and motor dexterity.[51] In our previous study of predictors of cognitive decline after the first lacunar stroke, vCI was registered in as many as 63.9% of patients 4 years later, indicating that the risk for cognitive decline persisted also in the medium/long-term follow-up period.[9] In a prospective study by Lawrence et al[53], the pattern of cognitive decline seen in SVD over 3 years was consistent with the pattern at baseline and the rate of decline was rather slow. Interestingly, vCI was more related to WMH lesions than to number of lacunes in our cohort, which is in contrast with findings of other authors.[52,54]

There are limitations to our study, including other potential confounding factors not analyzed, such as duration, severity and treatment of HT and other vascular risk factors, or imaging confounders for vCI, such as brain atrophy or microbleeds. It is also possible that additional factors not analyzed in our study were associated with SVD occurrence, such as homocysteine levels, genetic background, and in particular the differences in treatment of vascular RF. However, we report results on a well-defined cohort of SVD patients followed up prospectively, pointing to potentially different subpopulations of SVD patients in regard to common RF which should be targeted with different prevention and treatment strategies.

5 | CONCLUSION

In patients with SVD, HT contributes to poorer clinical outcome and more severe neuroradiological presentation.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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