ORIGINAL ARTICLE

Assessment of enlarged perivascular spaces and their relation to target organ damage and mild cognitive impairment in patients with hypertension

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Background and purpose: Enlarged perivascular spaces (EPVS) have been recently considered a feature of cerebral small vessel disease. They have been related to aging, hypertension and dementia but their relationship with hypertension related variables (i.e. target organ damage, treatment compliance) and mild cognitive impairment (MCI) is not fully elucidated. Our aims were to investigate the relation between basal ganglia (BG) and centrum semiovale (CSO) EPVS with vascular risk factors, hypertension related variables and MCI.

Methods: In all, 733 hypertensive individuals free of stroke and dementia from the Investigating Silent Strokes in Hypertensives, a magnetic resonance imaging Study (ISSYS) underwent brain magnetic resonance imaging and cognitive testing to diagnose MCI or normal cognitive aging.

Results: The numbers of participants presenting high grade (>10) EPVS at the BG and CSO were 23.3% and 40.0%, respectively. After controlling for vascular risk factors, high grade BG EPVS were associated with age (odds ratio 1.68; 95% confidence interval 1.37, 2.06), poor antihypertensive compliance (1.49; 1.03, 2.14) and the presence of microalbuminuria (1.95; 1.16, 3.28), whereas in the CSO only age (1.38; 1.18, 1.63) and male sex were associated with EPVS (1.73; 1. 24, 2.42). MCI was diagnosed in 9.3% of the participants and it was predicted by EPVS in the BG (1.87; 1.03, 3.39) but not in the CSO. This last association was greatly attenuated after correction for lacunes and white matter hyperintensities.

Conclusions: Basal ganglia EPVS are associated with the presence of microalbuminuria and poor adherence to antihypertensive drugs. The BG EPVS relation with MCI is not independent of the presence of other cerebral small vessel disease markers.

Background

Perivascular spaces have recently become an active area of study in the cerebral small vessel disease (cSVD) research field [1,2]. These spaces are located around perforating arteries of the brain, participate in the interstitial fluid recycle pathway and become visible in magnetic resonance imaging (MRI) when they

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enlarge. Enlarged perivascular spaces (EPVS) have been described in the presence of other brain MRI markers of cSVD as white matter hyperintensities (WMHs) and lacunes [3]. They are very common in the elderly and have been related to vascular risk factors (VRFs), especially hypertension [1].

Hypertension and other VRFs in mid-life are associated with mild cognitive impairment (MCI) which is the transitional status between normal cognitive aging and dementia [4]. Also, markers of cSVD are common in the elderly and have been related to cognitive impairment and dementia [5]. Besides, a few studies have found that EPVS are related to poor cognitive function and they might contribute to an increased dementia risk [6,7]. Little is known about the relation of MCI with EPVS [8].

In this study our aim was (i) to describe the presence of EPVS at different locations in asymptomatic hypertensive individuals and study their relation with other cSVD markers, VRFs and hypertension related target organ damage (TOD) markers and (ii) to determine whether their presence and location is different in MCI participants compared to those with normal cognitive aging (NCA).

Methods

Study population

Our study population is included within the ISSYS project (Investigating Silent Strokes in Hypertensives, a magnetic resonance imaging study). This is an ongoing observational, prospective study of 1037 essential hypertensive individuals aged 50–70 years old without previous clinical stroke or dementia, aimed to investigate the prevalence of silent cerebrovascular lesions and cognitive impairment. The participants were randomly selected from 14 primary care centers in the north area of Barcelona city. Our study protocol has been published previously elsewhere [9].

The study was conducted in accordance with the Helsinki Declaration and was approved by the local ethics committee; all participants gave their informed written consent prior to inclusion.

Brain magnetic resonance imaging

All participants underwent a brain MRI with the same 1.5 T MRI scanner [9]. EPVS were regarded as sharply delineated ovoid, round or linear structures depending on the imaging plane, size <3 mm, following the path of perforating arterioles, located in the basal ganglia (BG) and centrum semiovale (CSO) and with cerebral spinal fluid intensity signal in T2- and T1-weighted images. EPVS were rated with a previously published semi-quantitative score in each location taking into account the slice and the side with the highest number of EPVS. Scores for EPVS range from 0 (none), 1 (1−10), 2 (11−20), 3 (21−40) to 4 (>40) in each location [2]. Figure 1 shows examples of high grade EPVS in each location.

Apart from EPVS other markers of cSVD were rated [10] (see Appendix S1 for an extended explanation of brain MRI methodology).

Cognitive assessment

In this study, the data from 798 Caucasian Mediterranean participants who were literate and did not have health conditions interfering with cognitive function were analyzed. All participants were evaluated by means of the screening test Dementia Rating Scale second version (DRS-2). The DRS-2 is a screening

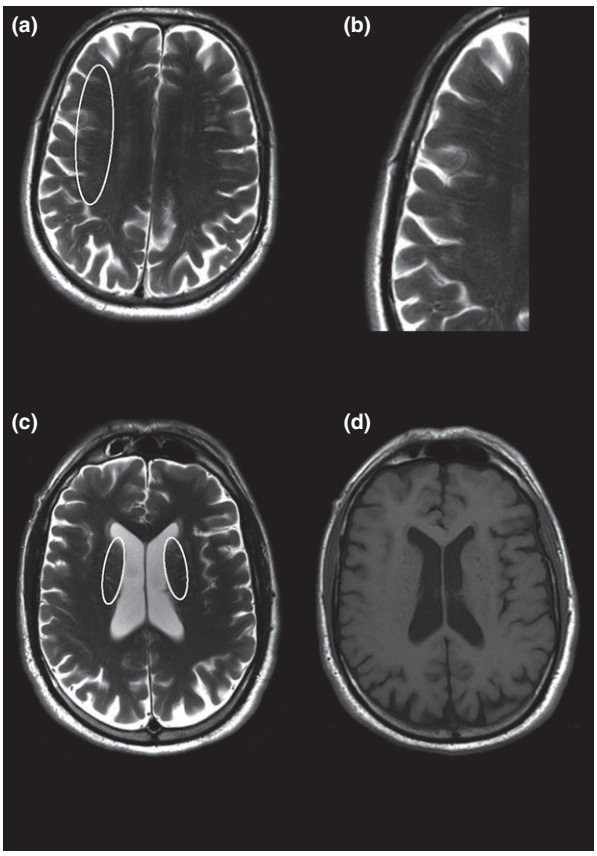

Figure 1 Examples of extensive enlarged perivascular spaces in MRI. (a) Extensive (>10) enlarged perivascular spaces in the centrum semiovale (lines in circle) in T2-weighted MRI; (b) magnification of the region indicated in (a). (c) Extensive enlarged perivascular spaces in the basal ganglia (lines and dots in circles) in T2-weighted MRI; (d) in T1-weighted MRI.

tool widely used in clinical and research settings for detection, differential diagnosis and follow-up of dementia [11]. Total DRS-2 raw scores were adjusted by age and education following a previously described methodology (range 2–18 points) [12].

All those participants with suspected cognitive impairment, namely DRS-2 adjusted by age and education ≤8 [11], were invited to undergo an extensive cognitive re-evaluation to establish cognitive diagnosis (n = 138) (see Appendix S1 for extended cognitive assessment explanation).

Mild cognitive impairment and normal cognitive aging diagnosis

The MCI diagnosis was assigned by consensus between the neurologist and neuropsychologist who visited the patients, following previously published criteria [13]. Briefly, MCI was considered in subjects who presented an acquired alteration of one or more cognitive domains that did not reach dementia level. This alteration lasted for months to years and was demonstrated on cognitive testing (performance mainly below 1.5 SD of the adjusted mean compared with the normative group). The basic activities of daily living were preserved and there was absent or minimal impairment in complex instrumental activities. Participants with a previous depression were considered for the present analysis if it was under treatment and controlled.

All those with normal results in the screening test (DRS-2 > 8) or who did not fulfill criteria for MCI were considered as having NCA.

Figure S1 shows the flowchart of the study, taking into account cognitive diagnosis and MRI acquisition.

Definition of covariates

Office blood pressure (BP) was calculated as the mean of the last two out of three measurements after 5 min rest. BP control was defined as optimal if BP was ≤140/90 and was defined as poor otherwise. Compliance with blood pressure lowering drugs (BPLDs) was assessed by the Morisky–Green scale. This is a four-question scale with yes/no answers and reflects the patient's attitude towards treatment. It is useful to find out whether the patient is a good complier and the causes for non-adherence [14].

Hypertension TOD markers were assessed for heart and kidney [15]. A 12-lead electrocardiogram was performed to assess signs of heart left ventricular hypertrophy (single measurement of R wave in the augmented vector left). Estimated kidney glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [16]. A single-spot urine sample was collected to study microalbuminuria which was defined as a urine albumin to creatinine ratio (UACR) ranging from 30 to 300 mg/g [15].

Total and high density lipoprotein cholesterol (HDL cholesterol) were measured on an automated clinical chemistry analyzer. Diabetes mellitus was defined as self-reported or confirmed by a clinical record history of diabetes in those under oral glucose lowering drugs or insulin or with HbA1c levels >7%. Smoking habit was defined as active or inactive.

Education was defined as the maximum years of formal education accomplished from childhood to early adulthood.

Statistical analysis

For the first aim, a univariate analysis was performed to relate the grade (high versus low grade) and localization of EPVS (BG or CSO) with VRFs, TOD and cSVD markers. EPVS were considered high grade when more than 10 lesions (≥ grade 2 in the rating scale) were present according to the median of the distribution of our data and to previous literature on stroke individuals [17]. Pearson's χ^2 was used for categorical variables and the t test or Mann–Whitney U test for continuous variables depending on their distribution. Then binary logistic regression models were performed to analyze the relation of high grade EPVS in the CSO and BG as outcomes with VRFs and hypertension TOD markers as determinants.

Secondly univariate and multivariate analyses were performed, taking as outcome the cognitive status (MCI versus NCA) and as determinants BG or CSO EPVS. These analyses were also adjusted by those factors associated with the presence of high grade EPVS and those factors related to cognitive status in our sample or that were previously established in the literature. The interaction terms between EPVS and WMHs (or lacunes) were tested but none was significant.

Results

Characteristics of the sample

The mean age of the sample was 62.8 years (±5.3) and half of them were men. The participants were long-standing hypertensive individuals (median duration 8 years, interquartile range 5–12) and almost all were taking BPLDs (98.1%), although only slightly more than half had good BP control (55.5%). Other

baseline characteristics of the study sample are shown in Table 1.

High grade BG EPVS were found in 23.3% of the participants and high grade CSO EPVS in 40.0%. The prevalence of EPVS by grades is shown in Table 2.

With regard to hypertension TOD, eGFR was 88.8 (78.1, 96.2) ml/min/1.73 m^2 and only two participants had very low eGFR (≤30 ml/min/1.73 m^2). It was shown that 12.1% of the participants had microalbuminuria and seven had proteinuria (UACR > 300 mg/g). Previous cardiovascular disease was found in 12.6% but only 8.7% had left ventricular hypertrophy.

Topography of EPVS and its relation with other cSVD lesions, VRFs and hypertension TOD

As shown in Fig. 2, high grade BG EPVS were related to the presence of lacunes and a higher grade of deep and periventricular WMHs ($P < 0.001$, in all comparisons). Also high grade CSO EPVS were related to lacunes and high grade WMHs ($P < 0.05$ in all cases).

Age, hypertension variables (BPLD use, BPLD poor compliance) and microalbuminuria were related to high grade BG EPVS in the univariate analysis (all $P < 0.05$) compared to low grade BG EPVS. Age,

Table 2 Distribution of enlarged perivascular spaces (EPVS)

EPVS grade (number EPVS)	Centrum semiovale (*N*, %)	Basal ganglia (*N*, %)
Grade 0 (none)	12 (1.7)	7 (1.1%)
Grade 1 (1–10)	425 (58.2)	555 (75.7)
Grade 2 (11–20)	238 (32.6)	133 (18.1)
Grade 3 (21–40)	50 (6.8)	34 (4.6)
Grade 4 (>40)	5 (0.7)	4 (0.5)

Missing data: centrum semiovale EPVS (three) due to technical problems.

Table 1 Characteristics of the sample

Characteristic	All (*N* = 733)	Mild cognitive impairment (*n* = 74)	Normal cognitive aging (*n* = 659)
Age, years	62.8 (5.3)	63.3 (5.5)	62.8 (5.3)
Sex, female	367.0 (50.0%)	41 (55.4%)	326 (49.5%)
Education, years	8.0 (7.0–12.0)	**8.0 (5.0–8.2)**	**8.0 (7.0–12.0)****
Diabetes mellitus	183 (24.9%)	22 (29.7%)	159 (24.2%)
Total cholesterol, mg/dl	217.5 (41.8)	221.0 (49.3)	217.1 (40.9)
HDL cholesterol, mg/dl	49.6 (13.4)	49.0 (15.1)	49.7 (13.2)
Current smoker	113 (15.4%)	12 (16.2%)	101 (15.3%)
Body mass index	29.9 (27.1, 32.9)	29.9 (26.4, 32.6)	29.9 (27.1, 32.9)
Systolic blood pressure, mmHg	142.4 (15.9)	143.0 (17.6)	142.3 (15.7)
Diastolic blood pressure, mmHg	77.4 (9.3)	75.4 (9.6)	77.7 (9.3)
Poor BP control (SBP > 140 or DBP > 90)	325 (44.5%)	24 (32.4%)	202 (30.8%)
Use of BPLDs	720 (98.1%)	69 (93.2%)	628 (95.3%)
Number of BPLDs	2.0 (1.0, 2.0)	34 (45.9%)	290 (44.0%)
Poor BPLD compliance	324 (44.2%)	24 (32.4%)	202 (30.8%)
Hypertension duration, years	8.0 (5.0, 12.0)	8.0 (6.0, 11.0)	8.0 (5.0, 12.0)
Brain MRI lesions			
High grade EPVS in CSO	294 (40.0%)	27 (37.0%)	266 (40.5%)
High grade EPVS in BG	172 (23.3%)	**24 (32.4%)**	**147 (22.3%)***
Lacunar infarcts	54 (7.4%)	8 (10.8%)	46 (7.0%)
High grade periventricular WMH	64 (8.7%)	10 (13.5%)	54 (8.2%)
High grade deep WMH	33 (4.5%)	**8 (10.8%)**	**25 (3.8%)****
Hypertension target organ damage			
CKD-EPI	88.8 (78.1, 96.2)	92.8 (80.0, 97.4)	88.7 (77.9, 95.7)
UACR	5.6 (3.6, 11.2)	7.0 (3.9, 12.8)	5.4 (3.5, 10.8)
Microalbuminuria	89 (12.1%)	11 (16.4%)	78 (12.4%)
Left ventricle hypertrophy	62 (8.7%)	9 (12.5%)	53 (8.3%)
Coronary heart disease	71 (9.7%)	5 (6.8%)	66 (10.0%)
Previous cardiovascular disease	92 (12.6%)	9 (12.5%)	83 (12.5%)

BG, basal ganglia; BP, blood pressure; BPLDs, blood pressure lowering drugs; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CSO, centrum semiovale; DBP, diastolic blood pressure; HDL cholesterol, high density lipoprotein cholesterol; high grade EPVS, high grade (>10 lesions) of enlarged perivascular spaces; high grade WMHs, white matter hyperintensities rated with the Fazekas scale corresponding to grade ≥2; MRI, magnetic resonance imaging; SBP, systolic blood pressure; UACR, urine to albumin creatinine ratio. For continuous variables mean (SD) or median (interquartile range) and for categorical variables count (%) is given. Bold values indicate $*P \leq 0.05$, $**P \leq 0.01$

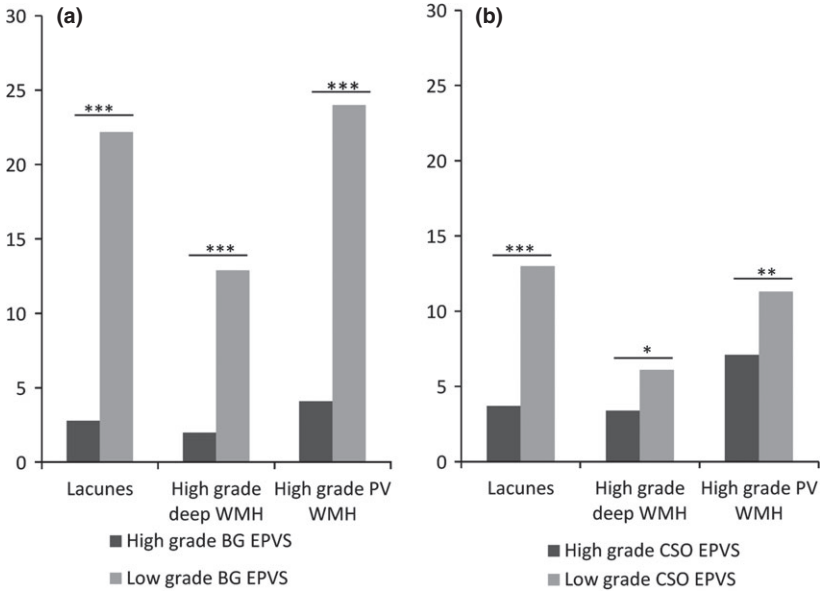

Figure 2 Relation between basal ganglia (BG) and centrum semiovale (CSO) enlarged perivascular spaces (EPVS) and other MRI cerebral small vessel disease markers. The *y* axis represents the percentage of lacunes, high grade deep and periventricular WMHs within high grade EPVS locations (a, BG; b, CSO). High grade WMHs, white matter hyperintensities grade ≥2 assessed by the Fazekas scale; high grade EPVS, >10 enlarged perivascular spaces. *$P < 0.1$; **$P < 0.05$; ***$P < 0.001$.

male sex, poor BP control and microalbuminuria were related to high grade CSO EPVS (all $P < 0.05$).

Then two multivariate analysis were performed, one with BG and the other with CSO EPVS as dependent variables and adjusted by age, sex, BP control, diabetes mellitus, total cholesterol, smoking habit, BPLD compliance, BPLD use, previous cardiovascular disease and microalbuminuria. Older age was independently associated with having high grade EPVS at both locations [odds ratio (OR) 1.68; 95% confidence interval (95% CI) 1.37, 2.06 for BG and 1.38; 1.18, 1.63 for CSO, both $P < 0.001$]. In the case of EPVS in the BG, also poor adherence to BPLDs (OR 1.49; 95% CI 1.03, 2.14) and microalbuminuria (OR 1.95; 95% CI 1.16, 3.28) were independently associated with high grade EPVS. As for EPVS in the CSO, also male sex independently predicted high grade lesions (1.73; 1.24, 2.42). These results are shown in Table 3.

Characteristics of cognitive groups

Seventy-four participants (9.3%) were diagnosed with MCI and 659 with NCA. As expected, MCI participants had fewer years of formal education than NCA participants [8 (5–8) vs. 8 (7–12), $P < 0.01$]. Table 1 gives other MCI and NCA comparisons.

For EPVS, those with MCI presented high grade BG EPVS more often than NCA subjects (32.4% vs. 22.3%, $P = 0.05$) but no differences were seen for high grade CSO EPVS between the two groups (40.5% vs. 37.0%, $P = 0.56$). Also MCI participants had a higher grade of deep WMHs than NCA subjects ($P = 0.01$). The multivariate analysis showed that high grade BG

Table 3 Association between hypertension related variables with EPVS localization

	High grade EPVS BG OR (95% CI)	*P*	High grade EPVS CSO OR (95% CI)	*P*
Age, per 5 years	**1.68 (1.37, 2.06)**	**< 0.001**	**1.38 (1.18, 1.63)**	**< 0.001**
Sex, male	1.17 (0.79, 1.73)	0.430	**1.73 (1.24, 2.42)**	**0.001**
Poor BP control	0.92 (0.64, 1.34)	0.671	1.24 (0.90, 1.71)	0.183
Diabetes mellitus	0.94 (0.75, 1.17)	0.584	0.93 (0.78, 1.13)	0.479
Total cholesterol, per SD increase	1.05 (0.86, 1.28)	0.625	1.07 (0.90, 1.26)	0.432
Active smoker	1.18 (0.70, 1.98)	0.534	0.92 (0.59, 1.44)	0.718
Poor BPLD compliance	**1.49 (1.03, 2.14)**	**0.032**	1.17 (0.85, 1.59)	0.337
BPLD use	2.82 (0.83, 9.61)	0.098	1.28 (0.59, 2.74)	0.527
Previous cardiovascular disease	1.12 (0.65, 1.95)	0.676	1.29 (0.80, 2.09)	0.308
Microalbuminuria	**1.95 (1.16, 3.28)**	**0.012**	1.44 (0.89, 2.33)	0.136

BG, basal ganglia; BP, blood pressure; BPLDs, blood pressure lowering drugs; CI, confidence interval; CSO, centrum semiovale; OR, odds ratio; EPVS, enlarged perivascular spaces. The analysis is adjusted by all covariates (age, sex, BP control, diabetes mellitus, total cholesterol, smoking habit, BPLD compliance, BPLD use, previous cardiovascular disease and microalbuminuria).

EPVS were associated with MCI (OR 1.88; 95% CI 1.03, 3.41) after controlling for other confounders that were related either to MCI in our previous studies (education, sex, diabetes mellitus) or with the presence of high grade BG EPVS (age, BPLD compliance and microalbuminuria). However, the relation between high grade BG EPVS and MCI disappeared when further adjustments were made for the presence of high grade deep WMHs and lacunes (1.59; 0.84, 3.01).

Discussion

A high prevalence of CSO and BG EPVS was found in our hypertensive cohort and a predominance of high grade CSO EPVS compared to BG EPVS (40.0% and 23.3%, respectively). Besides, MCI was related to BG EPVS after adjusting by VRFs but this relation disappeared after correcting for other cSVDs.

Our prevalence of high grade BG and CSO EPVS was almost double that described in a community-based study [7] but less prevalent than in a stroke cohort [18]. Thus, the setting where the study is conducted might lead to great differences in EPVS prevalence. Also differences might be observed in relation to different technical characteristics of MRI. Most of the studies used two-dimensional or three-dimensional 1.5 T MRI with varying slice thickness, interslice gap and sequence orientation, and a few used three-dimensional 3 T protocols that would improve EPVS quantification.

It was found that a higher grade of BG but not CSO EPVS was independently associated with poor BPLD compliance. Previous community-based studies also found stronger independent associations between BG EPVS and hypertension itself and/or BPLD use than with CSO EPVS [1,19].

Also microalbuminuria, a marker of kidney damage in hypertension, was associated with high grade BG EPVS. Previous studies also showed relations between EPVS and other features of cSVD (lacunes, WMHs and microbleeds) and microalbuminuria in community-based studies [20,21]. A recent study showed a relation between qualitatively assessed proteinuria and EPVS in both the CSO and BG in lacunar stroke patients [22]. However, to our knowledge the relation of BG EPVS with microalbuminuria in a community-based study is novel.

Small vessels in kidney and brain have similar anatomical and hemodynamic characteristics such as exposure to high flow volumes during the entire cardiac cycle and low vascular resistance [23]. Therefore, the effects of elevated BP in small arteries in kidney and brain might share similar mechanisms. Microalbuminuria also serves as a surrogate marker of kidney endothelial dysfunction. Endothelial dysfunction and protein leakage might impair perivascular space drainage as has been suggested in amyloid related diseases [24,25].

Our findings suggest a role for BG EPVS in MCI that is independent of VRFs and hypertension TOD markers but disappeared when adjusted by other cSVD markers. Previous recent studies also showed a role for BG EPVS in dementia and MCI. Two clinical studies showed that high grade BG EPVS were related to Alzheimer's disease and vascular dementia compared to NCA or frontotemporal dementia [26,27]. MCI was correlated with BG EPVS in the Alzheimer's Disease Neuroimaging Initiative project but also with CSO EPVS [8]. If anything, our study suggests a small contribution of BG EPVS to MCI that might not be separated from the effect of other cSVD markers such as white matter lesions or lacunes.

The strengths of this study are the relatively large sample size and the well characterized MCI group, coming from a unique random sample of hypertensive individuals. Similarly, a standard MRI protocol for the whole cohort was used. As limitations, a single-spot urine measurement to determine microalbuminuria was used that might have false positive results. Also the small number of participants in the extreme EPVS categories precluded other statistical approaches.

In conclusion, the present data show that EPVS in the BG and CSO are very common in hypertensive patients in the community. A higher grade of BG EPVS is associated with the presence of kidney organ damage and poor antihypertensive treatment compliance. The association between BG EPVS and MCI is not independent of the presence of other markers of cSVD, which often coexist with EPVS.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplemental methods.
Figure S1. Flowchart of the study.

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